Studies Directed Towards the Synthesis of (+)-Tricholomenyn B

A thesis submitted for the degree of Doctor of Philosophy
of the Australian National University

by

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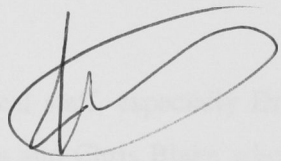
April, 2007

Declaration

I declare that, unless otherwise indicated, the material presented in this thesis represents the result of original work carried out by myself during the period 2002 – 2007 and has not been presented for examination for any other degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.



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April, 2007

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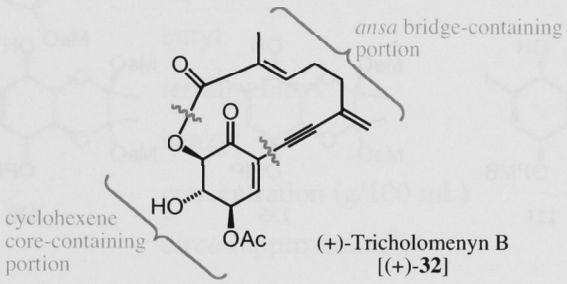
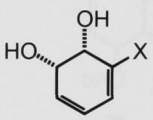
Abstract

(-)-Tricholomenyn B [(-)-**32**] is a highly oxygenated macrolide that has been isolated from the fungus *Tricholoma acerbum* and shown to possess anti-mitotic properties. This thesis covers work that was undertaken with the aim of developing a synthesis of (+)-tricholomenyn B using the enzymatically derived *cis*-diol **1** as starting material. Diols of the general type **1** can be readily obtained in high enantiomeric excess through the microbial oxidation of the appropriate halobenzene. A retrosynthetic analysis of tricholomenyn B revealed two key disconnections that divide the molecule into two sub-targets, namely the cyclohexene core-containing portion and the *ansa* bridge-containing fragment.

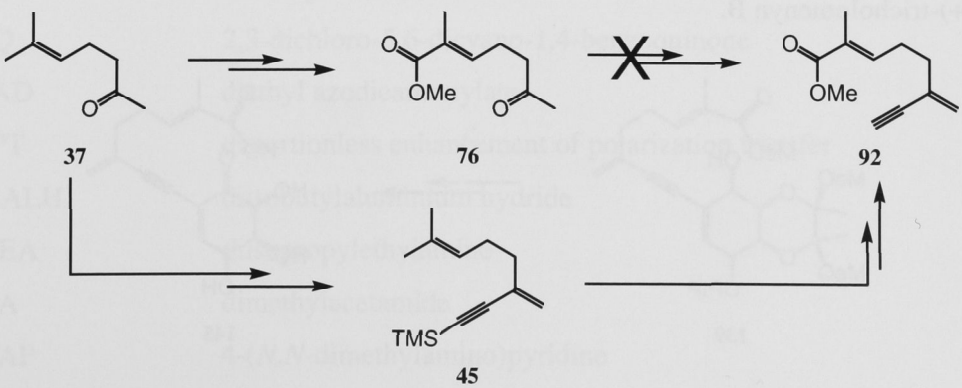


(+)-Tricholomenyn B
[(+)-**32**]

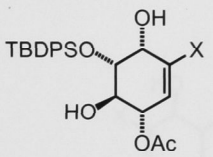


1
(X = I, Br)

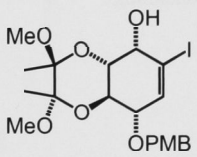
The synthesis of the *ansa* bridge-containing portion of the target molecule is described in Chapter Two. Thus, beginning with the commercially available ketone **37**, the initial approach focussed on preparing compound **76** using an *E*-selective selenium dioxide-mediated oxidation. Methyl ester **76**, however, resisted further elaboration to alkyne **92**. Accordingly, compound **45** was prepared from ketone **37** using established methods. Further manipulations, including a SeO_2-mediated allylic oxidation, then led to alkyne **92**.



Chapter Three describes the preparation of the cyclohexene core of (+)-tricholomenyn B *via* a reaction sequence that starts with *cis*-diol **1**. Three different protecting group strategies were investigated, involving the use of the differentially protected conduritols **98**, **111**, and **135**. The ultimately successful approach was that utilising compound **135**. Key features of this sequence include, (i), the exploitation of PIP (PIP = 3,4-methylenedioxybenzyl) as a novel alcohol protecting group and, (ii), a copper-catalysed Finkelstein-type reaction involving an alkenyl bromide. Also discussed in Chapter Three is work that culminated in a high-yielding Sonogashira cross-coupling reaction between alkenyl iodide **135** and alkyne **92** to give the product **139**.



98
X = Br, I



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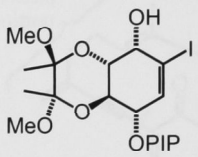
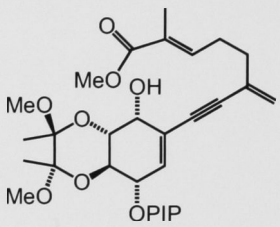
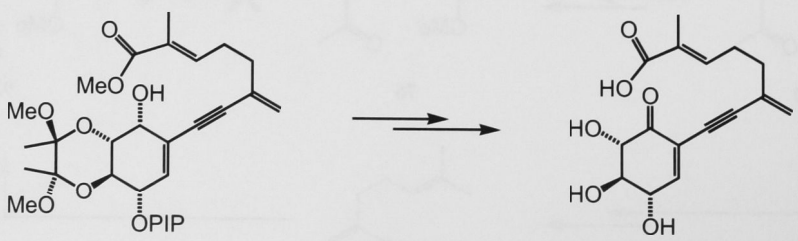


135



139

The continued elaboration of the intermediate **139** towards the final target (+)-**32** is described in Chapter Four. The oxidation of the allylic alcohol residue within the former compound followed by cleavage of the methyl ester could be accomplished quite readily. However, difficulties were encountered when attempting to remove the butane-diacetal group under conditions which left the PIP group intact. Accordingly, only triol **145** could be obtained but, disappointingly, this compound resisted further elaboration to the target compound (+)-**32**. The final section of this chapter suggests possible solutions to the problems encountered that could enable the completion of the synthesis of (+)-tricholomenyn B.



139 **145**

Glossary

The following abbreviations have been used throughout this thesis:

Å	Ångstrom
4-AcNH-TEMPO	4-acetamido-2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
AcOH	acetic acid
Ac	acetyl
Ac_2O	acetic anhydride
AIBN	2,2'-azobisisobutyronitrile
APT	attached proton test
aq.	aqueous
Bu	butyl
t-Bu	*tertiary*-butyl
Bn	benzyl
c	concentration (g/100 mL)
ca.	*circa* (approximately)
conc.	concentrated
COSY	homonuclear (^{1}H-^{1}H) correlation spectroscopy
m-CPBA	*m*-chloroperbenzoic acid
CSA	camphorsulfonic acid
δ	chemical shift (parts per million)
dba	dibenzylidine acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDO	dimethyldioxirane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement of polarization transfer
DIBALH	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane

DMF	*N,N*-dimethylformamide
2,2-DMP	2,2-dimethoxypropane
DPPA	diphenylphosphoryl azide
ee	enantiomeric excess
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EI	electron impact
eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
Et_3N	triethylamine
EtOH	ethanol
Et_2O or ether	diethyl ether
EtOAc	ethyl acetate
eV	electron volt
FGI	functional group interconversion(s)
g	gram
GC	gas chromatography
h	hour(s)
HMDS	hexamethyldisilazane
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
HSQC	heteronuclear single quantum correlation
Hz	Hertz
IR	infrared
i-Pr	*iso*-propyl
J	coupling constant (Hz)
LDA	lithium diisopropylamine
$M^{+\bullet}$	molecular ion (as encountered in EI MS)
Me	methyl
MeOH	methanol
MHz	Mega-Hertz
min	minute(s)

mol	mole
MOM	methoxymethyl
m.p.	melting point (°C)
MS	mass spectrum
MTM	methylthiomethyl
m/z	mass-to-charge ratio
NBS	*N*-bromosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
ORTEP	Oak Ridge Thermal Ellipsoid Plot
ν_{max}	infrared absorption maxima (cm^{-1})
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PIP	piperonyl
Ph	phenyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
R_f	retardation factor
SAR	structure-activity relationship
TBAF	tetra-*n*-butylammonium fluoride
TBDMS or TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TCA	trichloroacetic acid
TDO	toluene dioxygenase
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
triflate	trifluoromethanesulfonate
Ts	*p*-toluenesulfonyl or tosyl

p-TsOH	*p*-toluenesulfonic acid
W	Watts
<	less than
>	greater than
°C	degrees Celsius

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Chapter One

INTRODUCTION

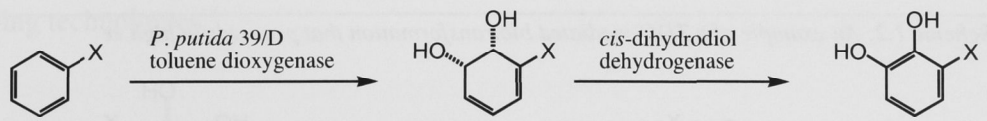
This chapter introduces microbially derived cis*-1,2-dihydrocatechols such as* ***1*** *and explores the development of their use in organic synthesis. The target molecule for the synthetic work described in later chapters, (+)-tricholomenyn B, is then discussed, as are plans to prepare it using diols of general type* ***1****.*

1.1 MICROBIALLY-DERIVED *CIS*-DIHYDROCATECHOLS AS STARTING MATERIALS IN ORGANIC SYNTHESIS

1.1.1 The biosynthetic origins of *cis*-dihydrocatechols

In 1968 Gibson *et al.* detailed their work on a mutant strain of *Pseudomonas putida* which, when grown on the appropriate aromatic substrate, accumulated the corresponding diol **1** (Scheme 1.1).[1] Further research established that diol **1**[*] is the first formed intermediate on the metabolic pathway by which aromatic compounds are eventually converted into pyruvate, a biologically significant molecule with a diverse range of fates within the cell.[2] The enzyme responsible for the production of diol **1** is toluene dioxygenase (TDO) and the *P. putida* strain studied by Gibson *et al.* lacked the *cis*-dihydrodiol dehydrogenase activity required to transform this initial metabolite into the corresponding catechol **2**. As a result, species **1** accumulated to sufficient levels such that it could be isolated from the fermentation mixture.[3,4]

Scheme 1.1*: Microbial oxidation of mononuclear-aromatic compounds*

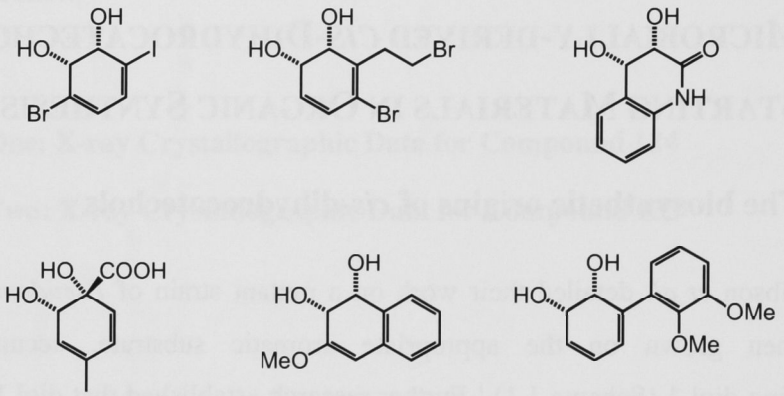


X = Me, H, F, Cl, Br, I **1** **2**

[*] Throughout this thesis, compounds of this type are referred to variously as diols, *cis*-diols, *cis*-dihydrocatechols and *cis*-1,2-dihydrocatechols.

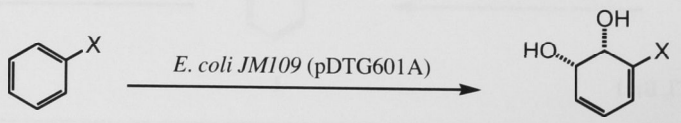
Since Gibson's original observations, a number of other dioxygenase enzymes have been identified. These types of enzymes are named after the substrate that they show the greatest affinity towards, with the toluene, biphenyl and naphthalene dioxygenases being the most well known members of the class. Despite their names, they are often capable of acting on a wide variety of substrates. Consequently, a large number of dioxygenase-derived *cis*-diol metabolites have now been isolated and characterised,[4] and a selection of these is shown in Figure 1.1. More comprehensive lists have been published in review articles by Boyd *et al.*,[4] Hudlicky *et al.*[5] and Johnson.[6]

***Figure 1.1**: A selection of microbially-derived* cis*-dihydrocatechols*



In more recent times, recombinant DNA techniques have led to the production of strains of bacteria that both over-express a specific dioxygenase enzyme and under-express *cis*-dihydrodiol dehydrogenases.[4] Consequently, large amounts of *cis*-dihydrocatechols can be produced using such genetically engineered micro-organisms, and so making these metabolites readily available for use as starting materials in chemical synthesis. As an example, a strain of *Eschericia coli* [JM109 (pDTG601)] has been developed which converts the relevant mono-substituted aromatic compound into the corresponding diol **1** at levels of up to 35 grams per litre of fermentation broth (Scheme 1.2).

***Scheme 1.2**: An example of a TDO-mediated biotransformation that proceeds in high ee*



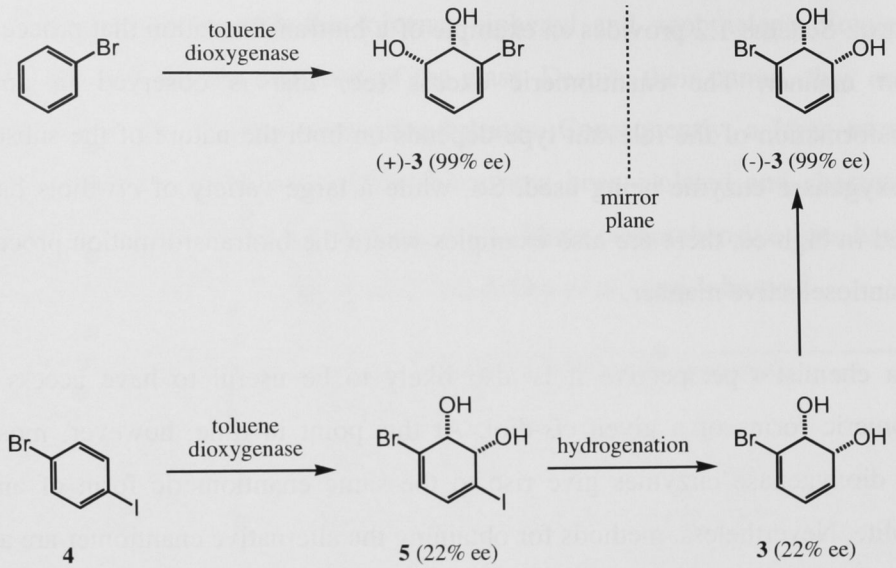
X = H, Me, I, Br, Cl

1
>99% ee

When considering the use of *cis*-dihydrocatechols as starting materials in organic synthesis, it is clearly advantageous to have these diols available in enantiomerically pure form. Scheme 1.2 provides an example of a biotransformation that proceeds in the relevant manner. The enantiomeric excess (ee) that is observed in any given biotransformation of the relevant type depends on both the nature of the substrate and the dioxygenase enzyme being used. So, while a large variety of *cis*-diols have been obtained in high ee, there are also examples where the biotransformation proceeds in a less enantioselective manner.

From a chemist's perspective it is also likely to be useful to have access to both enantiomeric forms of a given *cis*-diol. At this point in time, however, most of the known dioxygenase enzymes give rise to the same enantiomeric form of any given metabolite. Nevertheless, methods for obtaining the alternative enantiomer are available and these rely on the combined use of enzymatically-assisted kinetic resolution techniques and chemical manipulation of the *cis*-diol. Scheme 1.3 shows one such approach to the so-called "enantiomeric switching" that has been reported in the literature for obtaining both enantiomers of bromo-diol **3**.[7] Thus, TDO will oxidise bromobenzene directly to give the (+)-enantiomer of the bromo-diol [*viz.* (+)-**3**] in 99% ee, while the same enzyme will convert di-halo benzene **4** into the corresponding diol **5**, albeit in low ee. The iodo group within the last compound can then be removed using hydrogenolysis techniques and the resulting mixture of the (+)- and (-)-enantiomeric forms of compound **3** is then exposed to *cis*-diol dehydrogenase. The dehydrogenase enzyme selectively metabolises the (+)-enantiomer, leaving behind its optical antipode (-)-**3**, which is obtained in 99% ee. While this particular approach does suffer from the poor ee observed in the initial dihydroxylation step leading to compound **5**, this is an area in which great improvement seems possible, especially as additional dioxygenase enzymes continue to be isolated or generated through directed evolution and gene shuffling technologies.[8]

Scheme 1.3**: An "enantiomeric switching" regime that provides access to both enantiomeric forms of bromo-diol **3



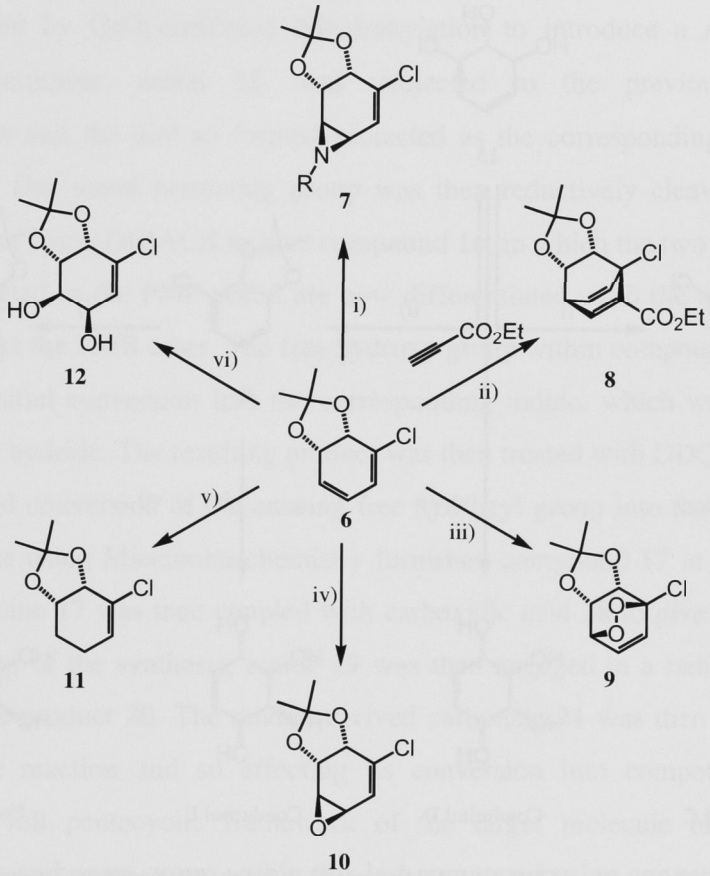
While a very large number of *cis*-dihydrocatechols have been obtained using biotransformations of the type just discussed, the work described in this thesis is primarily concerned with *cis*-diols obtained from the oxidation of mono-substituted benzenes of general type **1** (see Scheme 1.2, on page 2). The remainder of this introduction will, therefore, only deal with these types of *cis*-diols.

1.1.2 The synthetic utility of *cis*-dihydrocatechols

Microbially-derived *cis*-dihydrocatechols of the general type **1** are versatile starting materials that have been employed in a significant number of distinct bond-forming reactions. For example, through judicious choice of protecting groups, it is possible to direct reagent attack to one face of the *cis*-diol and so allowing stereochemically selective chemical manipulations of these chiral building blocks. Furthermore, as a result of the electron withdrawing effect exerted by halide substituents, the two alkenyl bonds within **1** (X = halogen) display very different reactivities. This makes it easy to selectively engage the non-halogenated alkenyl bond in various transformations, especially those involving external electrophiles. Some of the many bond-forming possibilities that the chloro-diol-derivative **6** can engage in are shown in Scheme 1.4. Thus, the diene moiety can participate in various Diels-Alder cycloaddition reactions to give adducts such as **8** and **9**, while the non-halogentated bond can act as a nucleophile

leading to, *inter alia*, aziridines (**7**), epoxides (**10**), dihydroderivatives (**11**) and diols (**12**).

***Scheme 1.4**: Selected chemical transformations of the acetonide derivative, **6**, of chloro-diol **1** (X = Cl)*

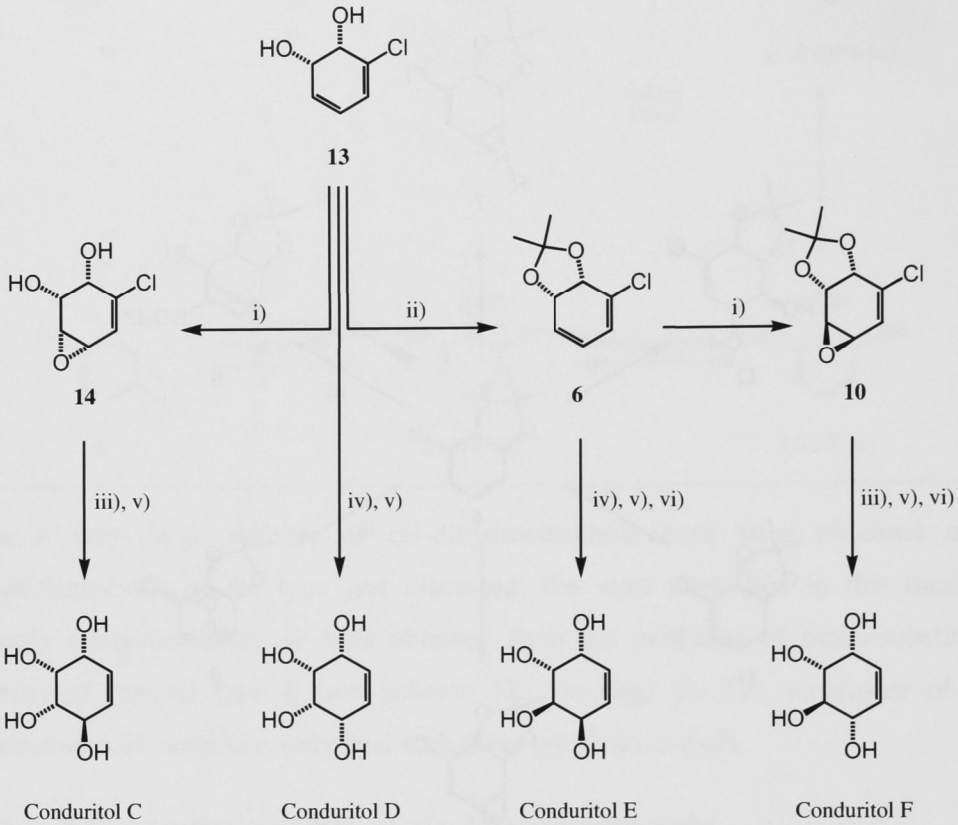


Chemical transformations: i) aziridination;[5] ii) Diels-Alder cycloaddition;[9] iii) singlet oxygen addition[10]; iv) epoxidation[10]; v) hydrogenation[11]; vi) dihydroxylation.[10]

Microbially-derived *cis*-dihydrocatechols have proven particularly useful in the synthesis of various conduritols. The conduritol family of compounds consists of all six possible diastereomeric forms of cyclohex-5-ene-1,2,3,4-tetraol. These stereoisomers are named conduritols A through to F, of which A and F have been found to occur in nature[12] and are important precursors to a number of glycoside inhibitors. The synthesis of conduritols C to F from a common starting material, *viz. cis*-diol **13**, exemplifies how this substrate can be manipulated in a stereochemically controlled way (Scheme 1.5). The required hydroxyl groups can be installed using either dihydroxylation or epoxidation/ring-opening sequences.[10,13] Alternating between use of the free diol **13** or the derived acetonide **6** means the stereochemistry of the dihydroxylation or

epoxidation/ring-opening reactions can be controlled, and so giving access to different conduritols as single diastereomers.

***Scheme 1.5**: Synthesis of conduritols C, D, E and F from the* cis*-1,2-dihydrocatechol **13**[10,13]*



Reagents and Conditions: i) *m*-CPBA (epoxidation); ii) 2,2-dimethoxypropane (protection); iii) H^+/H_2O (epoxide ring opening); iv) OsO_4 (dihydroxylation); v) Bu_3SnH/AIBN (halide cleavage); vi) H^+ (acetonide removal).

1.1.3 Selected natural product syntheses using *cis*-diols as starting materials

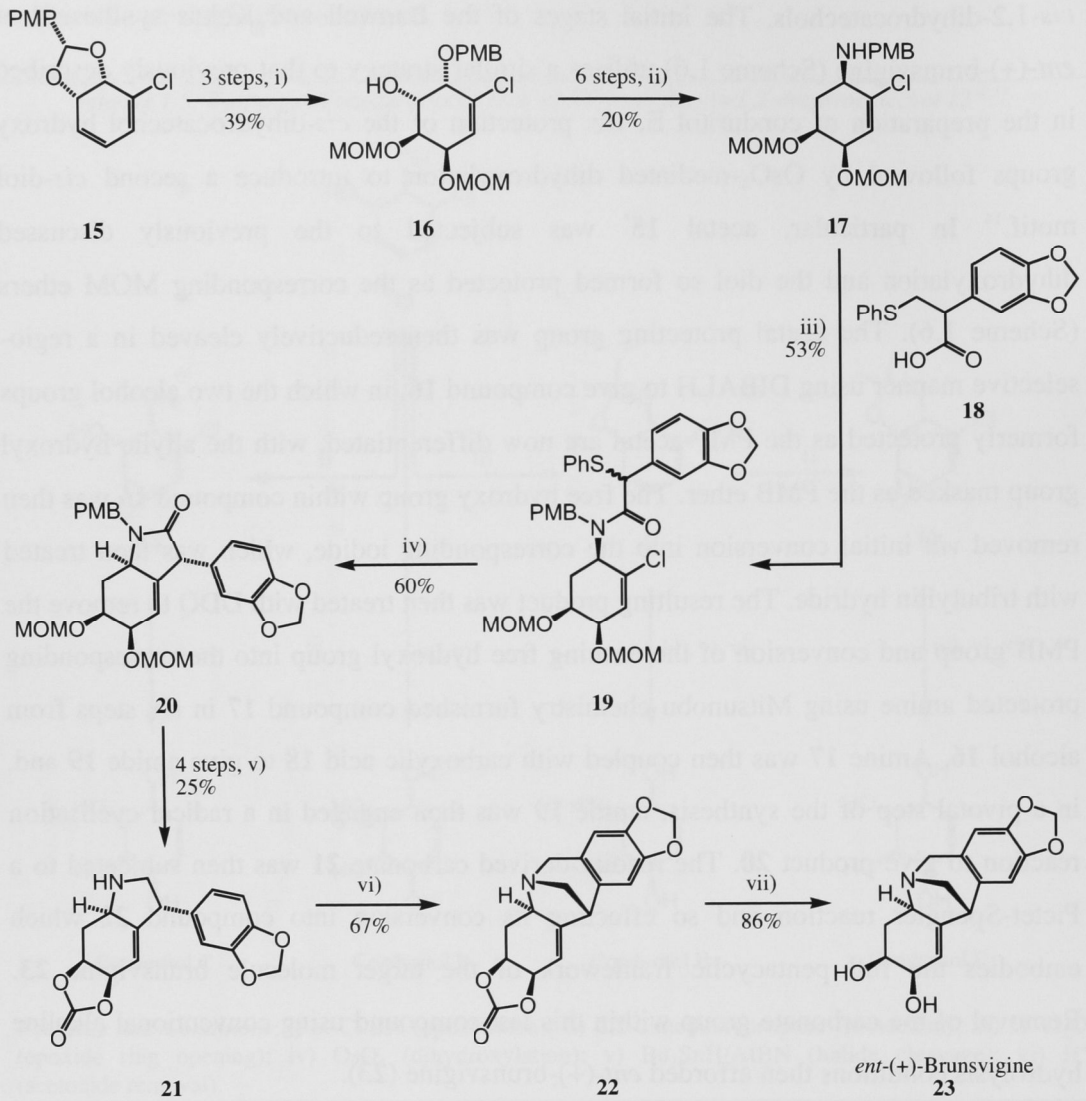
In addition to the synthesis of simpler and what might be described as "obvious" targets, such as the conduritols, *cis*-dihydrocatechols have been used in the preparation of a number of more structurally complex systems. In this section the remarkable scope and potential of *cis*-dihydrocatechols as synthons will be showcased through their recent application in the total synthesis of *ent*-(+)-brunsvigine[14] and (+)-hirsutic acid.[15]

(+)-Brunsvigine (**23**) is a member of a group of compounds known as the montanine alkaloids and contains a *cis*-diol moiety associated with a cyclohexene ring – a motif

that has proven to be readily accessible through the manipulation of *cis*-1,2-dihydrocatechols. The initial stages of the Banwell and Kokas synthesis[14] of *ent*-(+)-brunsvigine (Scheme 1.6) utilises a similar strategy to that previously described in the preparation of conduritol E, *viz.* protection of the *cis*-dihydrocatechol hydroxy groups followed by OsO_4-mediated dihydroxylation to introduce a second *cis*-diol motif.[14] In particular, acetal **15**[*] was subjected to the previously discussed dihydroxylation and the diol so formed protected as the corresponding MOM ethers (Scheme 1.6). The acetal protecting group was then reductively cleaved in a regio-selective manner using DIBALH to give compound **16**, in which the two alcohol groups formerly protected as the PMP-acetal are now differentiated, with the allylic hydroxyl group masked as the PMB ether. The free hydroxy group within compound **16** was then removed *via* initial conversion into the corresponding iodide, which was then treated with tributyltin hydride. The resulting product was then treated with DDQ to remove the PMB group and conversion of the ensuing free hydroxyl group into the corresponding protected amine using Mitsunobu chemistry furnished compound **17** in six steps from alcohol **16**. Amine **17** was then coupled with carboxylic acid **18** to give amide **19** and, in a pivotal step of the synthesis, amide **19** was then engaged in a radical cyclisation reaction to give product **20**. The readily derived carbonate **21** was then subjected to a Pictet-Spengler reaction and so effecting its conversion into compound **22** which embodies the full pentacyclic framework of the target molecule brunsvigine **23**. Removal of the carbonate group within this last compound using conventional alkaline hydrolysis conditions then afforded *ent*-(+)-brunsvigine (**23**).

[*] Acetal **15** was prepared in one step from chloro-diol **13**.

***Scheme 1.6**: Banwell and Kokas total synthesis of* ent-*(+)-brunsvigine (**23**)*

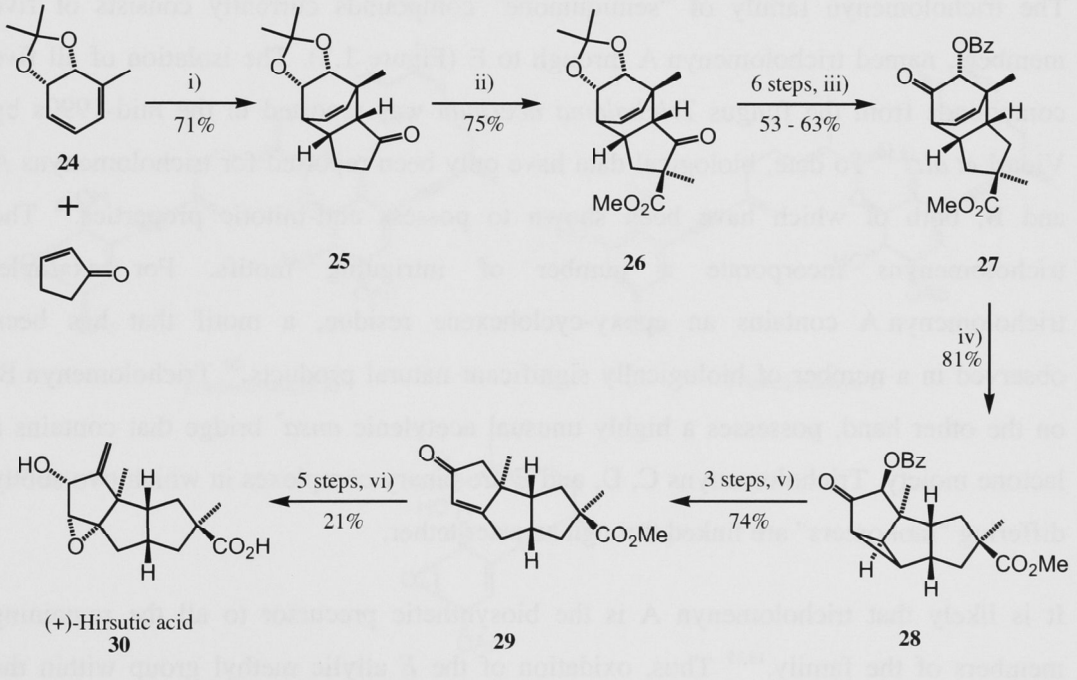


Reagents and Conditions: i) a) OsO_4, NMO, 63%; b) MOMCl, NaH, 88%; c) DIBALH, 71%; ii) a) triiodoimidazole, imidazole, PPh_3, 59%; b) *n*-Bu_3SnH, Et_3B, O_2, 84%; c) DDQ, 98%; d) DPPA, DEAD, PPh_3, 75%; e) PPh_3, H_2O/THF, 98%; f) *p*-$MeOC_6H_4CHO$ then $NaBH_3CN$, 56%; iii) EDCI, HOBt, DIPEA, 53%; iv) *n*-Bu_3SnH, *n*-Bu_6Sn_2, AIBN, 60%; v) a) $LiAlH_4$, $AlCl_3$ 94%; b) HCl, MeOH, 73%; c) triphosgene; d) HCl, H_2O, 36% (two steps); vi) $(H_2CO)_n$, HCO_2H, 67%; vii) KOH, MeOH, 86%.

While the *cis*-diol-containing cyclohexene motif of brunsvigine strongly hinted at the possible usefulness of *cis*-dihydrocatechols as precursors to this natural product, other (less obvious) carbon frameworks have also been prepared from the *cis*-1,2-dihydrocatechols. One such example is the recent total synthesis of (+)-hirsutic acid (**30**) from toluene diol-derivative **24** (Scheme 1.7).[15,16] Thus, tricycle **25** was prepared from compound **24** and cyclopentenone *via* a Diels-Alder cycloaddition reaction that proceeds in an *endo*-fashion, with the steric demands of the acetonide

group controlling the face of diene **24** at which the cycloaddition reaction takes place. Adduct **25** was then functionalised to give compound **26** and removal of the acetonide group followed by manipulation of the diol functionality furnished ketone **27**. In a key step, this last compound underwent a photo-assisted oxa-di-π-methane rearrangement with accompanying epimerisation of the benzyloxy group to give tetracycle **28**. Reductive cleavage and dehydrogenation of compound **28** afforded the previously reported enone **29**,[17] which was then elaborated to (+)-hirsutic acid **30** by installation of the exo-cyclic double bond, epoxidation of the internal double bond and reduction of the ketone moiety. The ketone-containing precursor to the final target **30**, which was formed in this last sequence, is also a natural product called (-)-complicatic acid.

***Scheme 1.7**: Austin, Banwell and Harfoot total synthesis of (+)-hirsutic acid (**30**)*



Reagents and Conditions: i) DCM, 19 kbar, 18 °C, 24 h, 71%; ii) LiHMDS, MeI, THF, 0 → 18 °C, then LiHMDS, MeO_2CCN, THF, 0 → 18 °C, 75%; iii) a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 → 18 °C, 99%; b) NaHMDS, CS_2, MeI, THF, 0 → 18 °C; c) *n*-Bu_3SnH, AIBN, toluene, 112 °C, 95% (over two steps); d) Dowex-50 resin, MeOH/H_2O, 80°C, 3 - 5 days, 76 – 90%; e) 4-AcNH-TEMPO, *p*-TsOH·H_2O, DCM, 0 → 18 °C; f) BzCl, Et_3N, DMAP, DCM, 0 → 18 °C, 74% (over two steps); iv) *hν*, acetophenone, acetone, 0 °C, 5 d, 81%; v) a) SmI_2, THF/MeOH, –78 °C; b) *n*-Bu_3SnH, AIBN, benzene, 80 °C, 87% (over two steps); c) TMSOTf, 2,6-lutidine, DCM, 0 → 18 °C, then $Pd(OAc)_2$, MeCN, 18 °C, then H_3O^+, 85%; vi) a) LiHMDS, Eschenmoser's salt, THF, –78 → 18 °C, 79%; b) MeI, Et_2O/DCM, 18 °C then basic alumina, DCM, 18 °C, 76%; c) LiI, DMF, 153 °C, 73%; d) H_2O_2, NaOH, MeOH/H_2O, –50 → 36 °C; e) $NaBH_3$, –35 → 0 °C, 46% (two steps).

Given the accessibility of large amounts of enantiomerically pure *cis*-dihydrocatechols and their proven usefulness in the preparation of complex natural products, these

enzymatically-derived diols are clearly attractive building blocks for organic synthesis. Indeed, one target for which the *cis*-diols seem to be ideal starting materials, is the highly oxygenated macrolactone tricholomenyn B – the subject of this thesis. Accordingly, the remainder of this chapter will deal with tricholomenyn B and related compounds, as well as providing background work pertinent to the central aim of this thesis, namely the development of a total synthesis of tricholomenyn B.

1.2 THE TRICHOLOMENYN FAMILY AND RELATED COMPOUNDS

1.2.1 Isolation

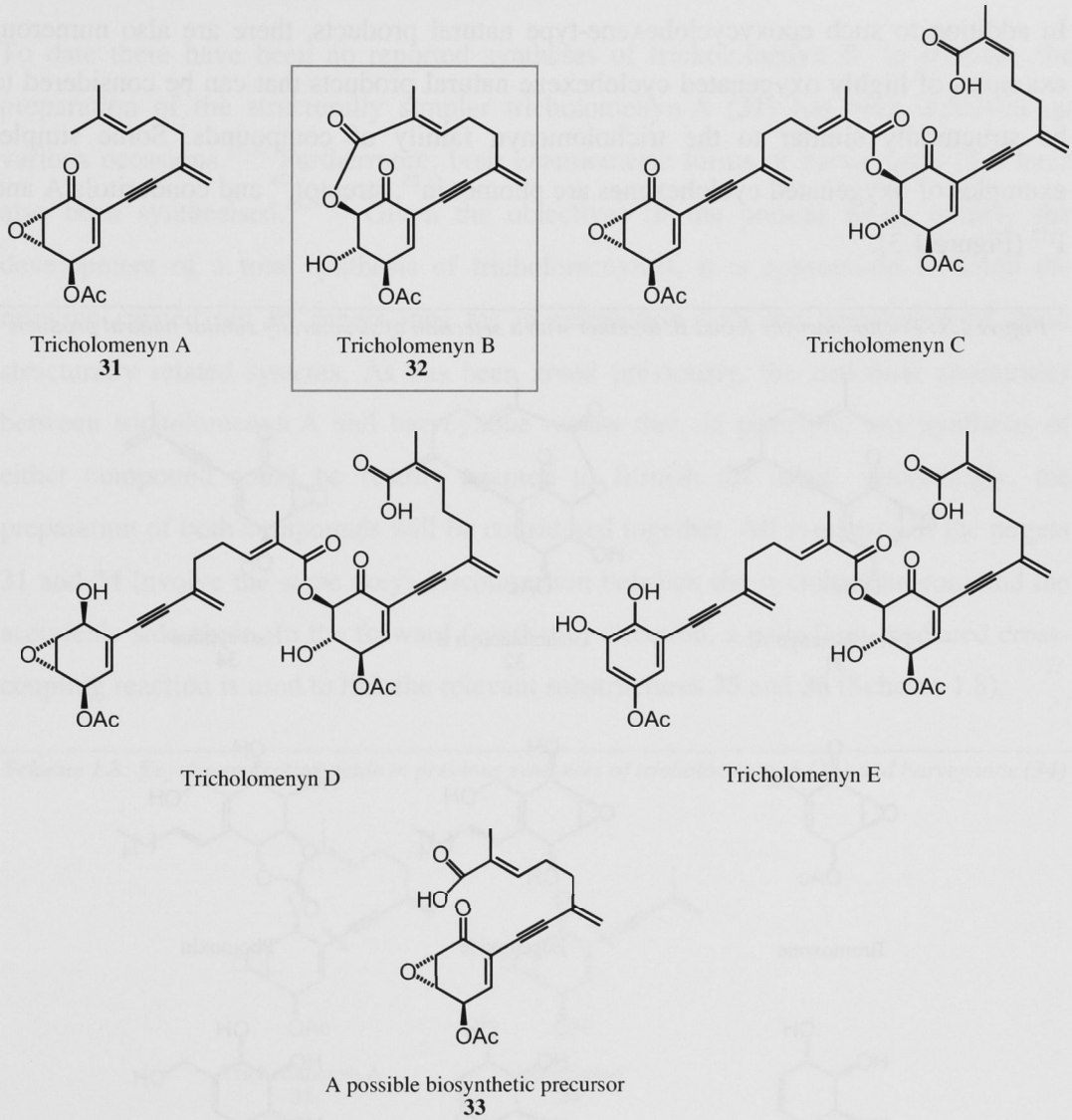
The tricholomenyn family of "semiquinone" compounds currently consists of five members, named tricholomenyn A through to E (Figure 1.2). The isolation of all five compounds from the fungus *Tricholoma acerbum* was reported in the mid-1990s by Vidari *et al.*[18,19] To date, biological data have only been reported for tricholomenyns A and B, both of which have been shown to possess anti-mitotic properties.[18] The tricholomenyns incorporate a number of intriguing motifs. For example, tricholomenyn A contains an epoxy-cyclohexene residue, a motif that has been observed in a number of biologically significant natural products.[20] Tricholomenyn B, on the other hand, possesses a highly unusual acetylenic *ansa*[*] bridge that contains a lactone moiety. Tricholomenyns C, D, and E are binary complexes in which two subtly differing "monomers" are linked through an ester tether.

It is likely that tricholomenyn A is the biosynthetic precursor to all the remaining members of the family.[18,19] Thus, oxidation of the *E* allylic methyl group within the tricholomenyn A side-chain would lead to a species such as carboxylic acid **33**, that could then participate in an *intra*-molecular nucleophilic ring opening of the attached epoxide moiety to deliver tricholomenyn B. If, on the other hand, species **33** were to participate in a similar process but now in an *inter*-molecular fashion and involving another molecule of epoxide **33**, then this would lead to tricholomenyn C. Tricholomenyns D and E could be derived from minor changes to tricholomenyn C, or

[*] The term *ansa* bridge is used in this context to refer to an aliphatic chain which is linked at either end to a single cyclic system.

from a modified form of compound **33** engaging in an intermolecular variation of the above-mentioned epoxide ring-opening process.

***Figure 1.2**: The tricholomenyn family of compounds and a possible biosynthetic precursor (**33**) to tricholomenyns B to E*



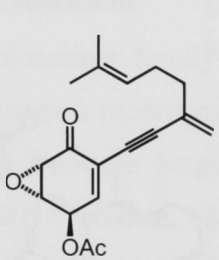
1.2.2 Other structurally related natural products

In the literature, there are many examples of compounds which bear structural similarities to members of the tricholomenyn family, including epoxycyclohexenes which possess a closely related core structure, such as bromoxone,[21] eupenoxide[22] and harveynone (**34**) (Figure 1.3).[20] Harveynone is of particular interest due to the strong structural relationship it has with tricholomenyn A. Indeed, as will be discussed in the

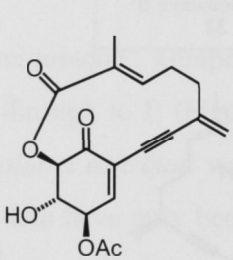
next section of this chapter, any synthesis of tricholomenyn A can be readily adapted to the synthesis of harveynone and *vice versa*. Harveynone occurs in nature in both enantiomeric forms, with the (+)-isomer possessing phytotoxic properties[23] while its optical antipode displays anti-tumour activity.[24]

In addition to such epoxycyclohexene-type natural products, there are also numerous examples of highly oxygenated cyclohexene natural products that can be considered to be structurally similar to the tricholomenyn family of compounds. Some simpler examples of oxygenated cyclohexenes are phomoxin[25], streptol,[26] and conduritols A and F[12] (Figure 1.3).

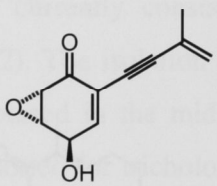
***Figure 1.3**: Tricholomenyns A and B, together with a selection of structurally similar natural products*



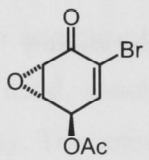
Tricholomenyn A
31



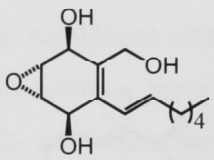
Tricholomenyn B
32



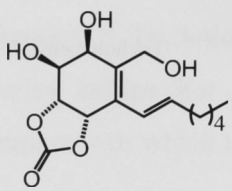
Harveynone
34



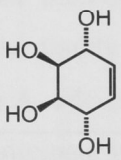
Bromoxone



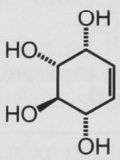
Eupenoxide



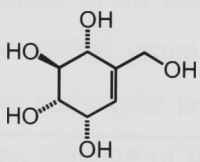
Phomoxin



Conduritol A



Conduritol F



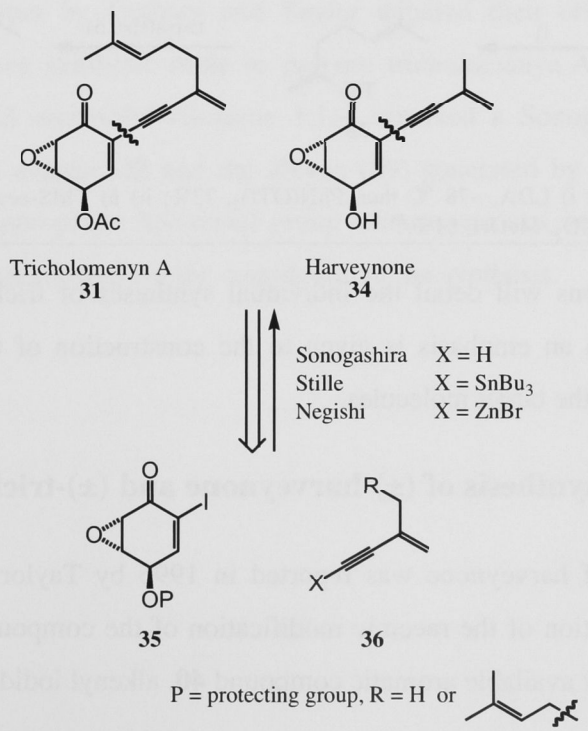
Streptol

1.3 Previous Syntheses Of Tricholomenyn A and Harveynone

1.3.1 General comments

To date there have been no reported syntheses of tricholomenyn B. In contrast, the preparation of the structurally simpler tricholomenyn A (**31**) has been achieved on various occasions.[27-30] Furthermore, both enantiomeric forms of harveynone (**34**) have also been synthesised.[28,30-34] Given the objectives of the present work, namely the development of a total synthesis of tricholomenyn B, it is appropriate to detail the research carried out by others thus far in connection with the preparation of these structurally related systems. As has been noted previously, the structural similarities between tricholomenyn A and harveynone means that, in principle, any synthesis of either compound could be readily adapted to furnish the other. Accordingly, the preparation of both compounds will be considered together. All syntheses of the targets **31** and **34** involve the same (key) disconnection between the cyclohexene core and the acetylenic side chain. In the forward (synthetic) direction, a palladium-mediated cross-coupling reaction is used to link the relevant substructures **35** and **36** (Scheme 1.8).

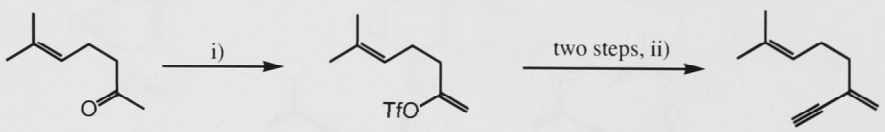
***Scheme 1.8**: Key disconnection made in previous syntheses of tricholomenyn A (**31**) and harveynone (**34**)*



Thus, previous syntheses of tricholomenyn A and harveynone all follow a similar general format, that is, involving separate preparations of the acetylenic side-chain and the cyclohexene core. This is followed by application of the aforementioned palladium-mediated cross-coupling reaction to join these precursor fragments of the target molecule. The synthesis is then completed using generally straightforward manipulations. The points of difference between the various syntheses of tricholomenyn A (**31**) and harveynone (**34**) lie in the construction of the cyclohexene core **35**, and the choice of palladium-mediated cross-coupling reaction.

The acetylenic portion of the target molecules is prepared in a similar general fashion in all syntheses. In the case of tricholomenyn A, for example, the side-chain is prepared by treating ketone **37** with base and trapping the resulting enolate as the triflate to give compound **38** (Scheme 1.9). Sonogashira cross-coupling of this last species with trimethylsilyl acetylene follows, and subsequent removal of the trimethylsilyl group then gives alkyne **39**. The side-chain of harveynone (2-methyl-1-buten-3-yne) is commercially available. If required, such alkynes can be converted into the corresponding alkynyl stannane or zinc bromide immediately prior to the coupling reaction.

***Scheme 1.9**: Preparation of the acetylenic side-chain of tricholomenyn A*



37 **38** **39**

Reagents and Conditions: i) LDA, –78 °C then $PhN(OTf)_2$, 73%; ii) a) TMS-acetylene, $PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, 88%; b) K_2CO_3, MeOH, 81%.[28]

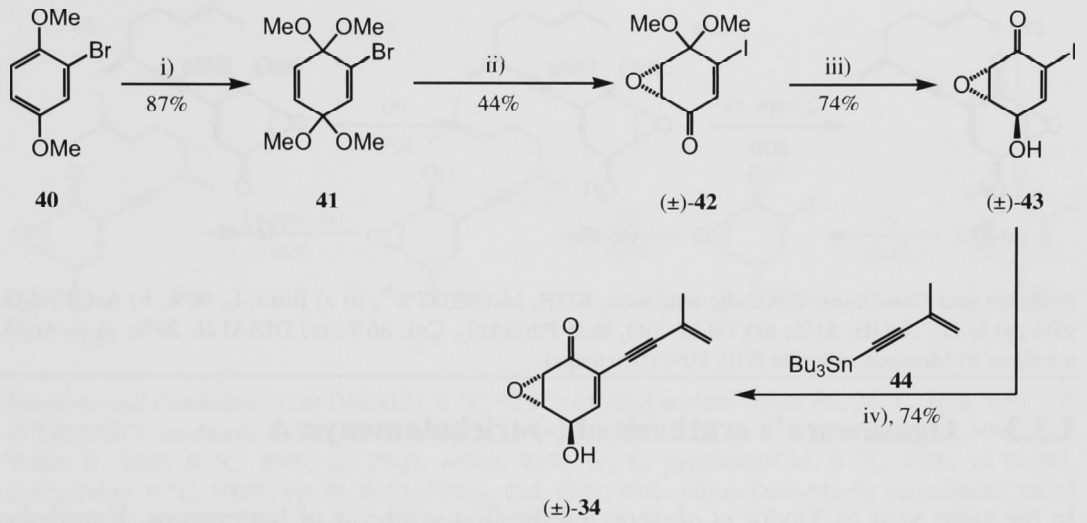
The next three sections will detail the individual syntheses of tricholomenyn A and harveynone, although an emphasis is given to the construction of the cyclohexenyl-containing portion of the target molecules.

1.3.2 Taylor's synthesis of (±)-harveynone and (±)-tricholomenyn A

The first synthesis of harveynone was reported in 1996 by Taylor *et al.*,[32] and this described the preparation of the racemic modification of the compound. Thus, starting with the commercially available aromatic compound **40**, alkenyl iodide **43** was accessed

in six steps and *via* a route that included an anodic oxidation (Scheme 1.10). Attempts to carry out the Sonogashira cross-coupling of alkenyl iodide **43** and 2-methyl-1-buten-3-yne were unsuccessful. In contrast, conversion of the terminal alkyne into the corresponding alkynyl-stannane (**44**) allowed for a successful Stille cross-coupling reaction to be carried out and so giving (±)-harveynone (**34**) directly.

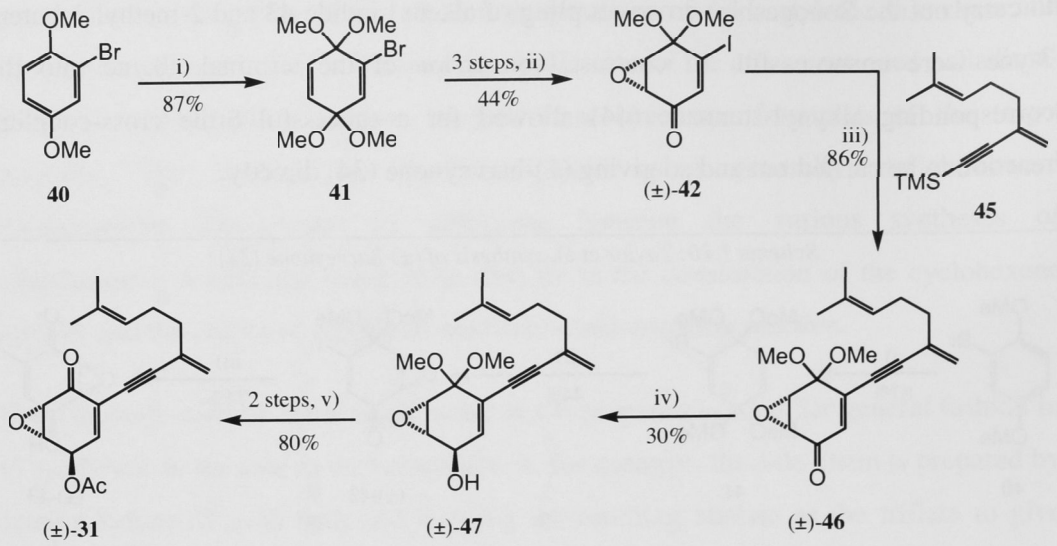
***Scheme 1.10**: Taylor* et al. *synthesis of (±)-harveynone (**34**)*



Reagents and Conditions: i) Anodic oxidation, KOH, MeOH, 87%[35]; ii) a) BuLi, I_2, 90%; b) AcOH/H_2), 95%; c) H_2O_2, NaOH, 51%; iii) a) DIBALH, THF, –78 °C; b) Montmorillonite K10, 74% (over two steps); iv) $PdCl_2(PPh_3)_2$, CuI, THF, 74%.

A subsequent paper by Graham and Taylor detailed their efforts directed towards adapting the above synthetic route to prepare tricholomenyn A.[29] The approach that eventually proved successful (Scheme 1.11) involved a Sonogashira cross-coupling reaction between diacetal **42** and the alkyne (**39**) generated by *in situ* desilylation of compound **45**. Appropriate functional group interconversions were then applied to the product (±)-**46** that allowed for the completion of the synthesis.

***Scheme 1.11**: Graham and Taylor synthesis of (±)-tricholomenyn A (**31**)*



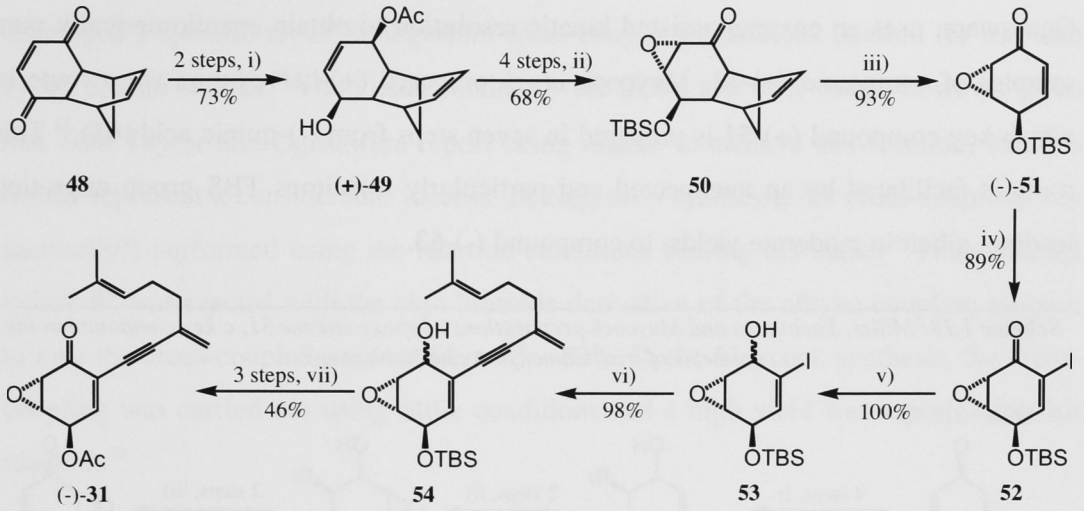
Reagents and Conditions: i) Anodic oxidation, KOH, MeOH, 87%[35]; ii) a) BuLi, I_2, 90%; b) AcOH/H_2O, 95%; c) H_2O_2, NaOH, 51%; iii) TBAF-SiO_2 then $Pd(OAc)_2$, CuI, 86%; iv) DIBALH, 30%; v) a) Ac_2O, pyridine; b) Montomorillonite K10, 80% (two steps).

1.3.3 Ogasawara's synthesis of (-)-tricholomenyn A

In the same year as Taylor *et al.* reported the first synthesis of harveynone, Kamikubo and Ogasawara also published the first synthesis of (-)-tricholomenyn A (Scheme 1.12).[27] The Ogasawara synthesis of tricholomenyn A commences with the Diels-Alder adduct, **48**, of benzoquinone and cyclopentadiene. The corresponding and readily derived *meso*-1,4-diol was then treated with lipase PS to give mono-acetate (+)-**49**. The long reaction time (16 days) required for this enzymatic resolution step was offset by the excellent ee (>99%) obtained. Further elaboration of enantiomerically pure acetate (+)-**49** gave epoxide **50**, which was subjected to a retro-Diels-Alder reaction to give the key intermediate (-)-**51** which was then iodinated using Johnson's conditions to give α-iodo-enone **52**. This last compound is the protected and enantiomerically pure form of the corresponding enone **43**, an intermediate in Taylor's synthesis of harveynone. In keeping with the observations made by Graham and Taylor, the Sonogashira cross-coupling of α-iodo-eneone **52** and alkyne **39** failed, while the corresponding Stille cross-coupling reaction was inefficient. However, by reducing the ketone of α-iodo-enone **52** to the corresponding alcohol **53**, a successful Sonogashira cross-coupling with alkyne **39** was achieved giving enyne **54**. Compound **54** was then elaborated to (-)-tricholomenyn A (**31**) in three steps by oxidising the allylic alcohol to the corresponding

ketone, removing the TBS group and, finally, acetylating the newly formed hydroxyl group.

***Scheme 1.12**: Kamikubo and Ogasawara synthesis of (-)-tricholomenyn A*



Reagents and Conditions: i) a) DIBALH, 0 °C, 92%[36]; b) vinyl acetate, lipase PS, 28 °C, 16 d, 79%[37]; ii) a) TBDMSCl, imidazole, DMF, 88%; b) K_2CO_3, MeOH; c) PDC, DCM, 87% (two steps); d) 30% H_2O_2, Triton B, THF, 0 °C, 89%; iii) Ph_2O, reflux, 93%; iv) I_2, pyridine/DCM, 0 °C, 89%; v) $NaBH_4$, $CeCl_3 \bullet 7H_2O$, 0 °C, 100%; vi) **39**, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 98%; vii) a) Dess-Martin periodinane, DCM, 90%; b) 46% HF/MeCN, 86%; c) Ac_2O, pyridine/DCM, 0 °C, 59%.

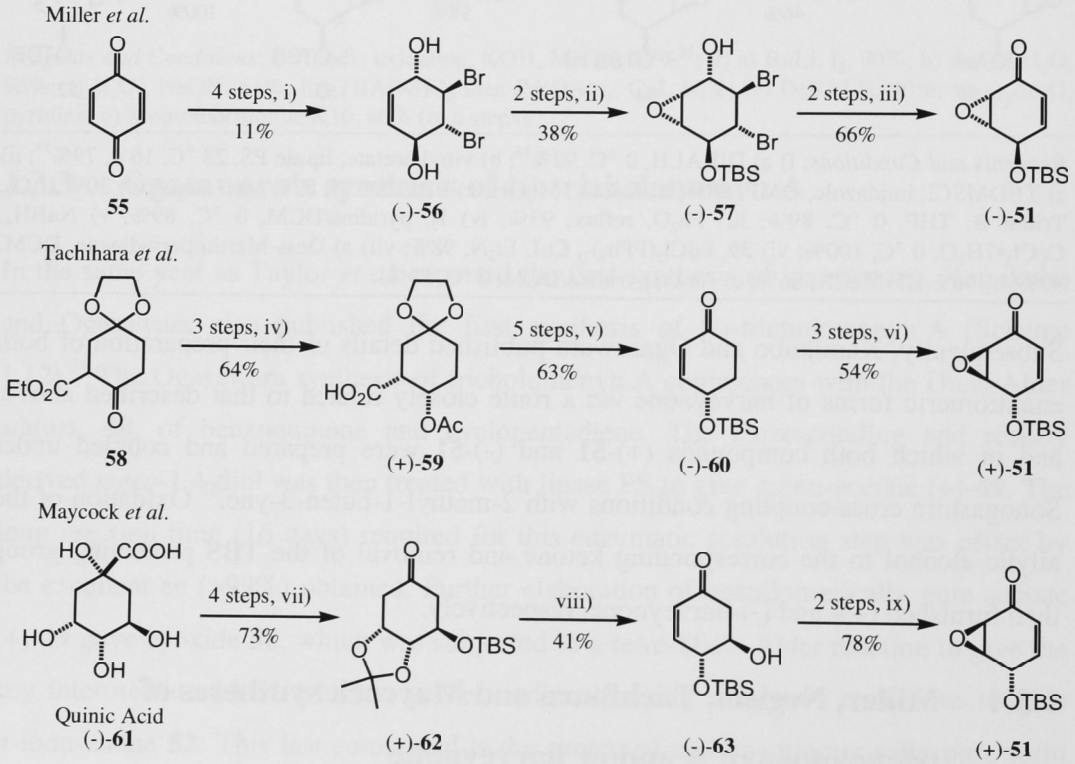
Subsequently, Kamikubo and Ogasawara published details of their preparation of both enantiomeric forms of harveynone *via* a route closely related to that described above, and in which both compounds (+)-**51** and (-)-**51** were prepared and coupled under Sonogashira cross-coupling conditions with 2-methyl-1-buten-3-yne.[31] Oxidation of the allylic alcohol to the corresponding ketone and removal of the TBS protecting group then furnished (+)- and (-)-harveynone, respectively.

1.3.4 Miller, Negishi, Tachihara and Maycock syntheses of tricholomenyn A and/or harveynone

Four other groups have also reported syntheses of tricholomenyn A and/or harveynone, namely those headed by Miller, Negishi, Tachihara and Maycock. These syntheses (Scheme 1.13) all proceed *via* the same key compound **51**, that was employed by Kamikubo and Ogasawara. Miller *et al.* prepared the epoxide (-)-**51** in a nine-step sequence featuring a lipase-assisted kinetic resolution to give the enantiomer required for the preparation of (-)-tricholomenyn A and (-)-harveynone.[28] Negishi prepared

intermediate (±)-**51** by a route that very closely mirrors that of Miller *et al.* but lacks the kinetic resolution step.[30] Tachihara *et al.* reported the preparation of compound (+)-**51**, the acquisition of which constitutes a formal total synthesis of (+)-harveynone and *ent*-(+)-tricholomenyn A.[34] The Tachihara synthesis, like those of Miller and Ogasawara, uses an enzyme-assisted kinetic resolution to obtain enantiomerically pure samples of compound (+)-**51**. Maycock *et al.* prepared (+)-harveynone *via* a route in which key compound (+)-**51** is prepared in seven steps from (-)-quinic acid (**61**).[33] This route is facilitated by an unexpected and particularly fortuitous TBS group migration leading, albeit in moderate yields, to compound (-)-**63**.

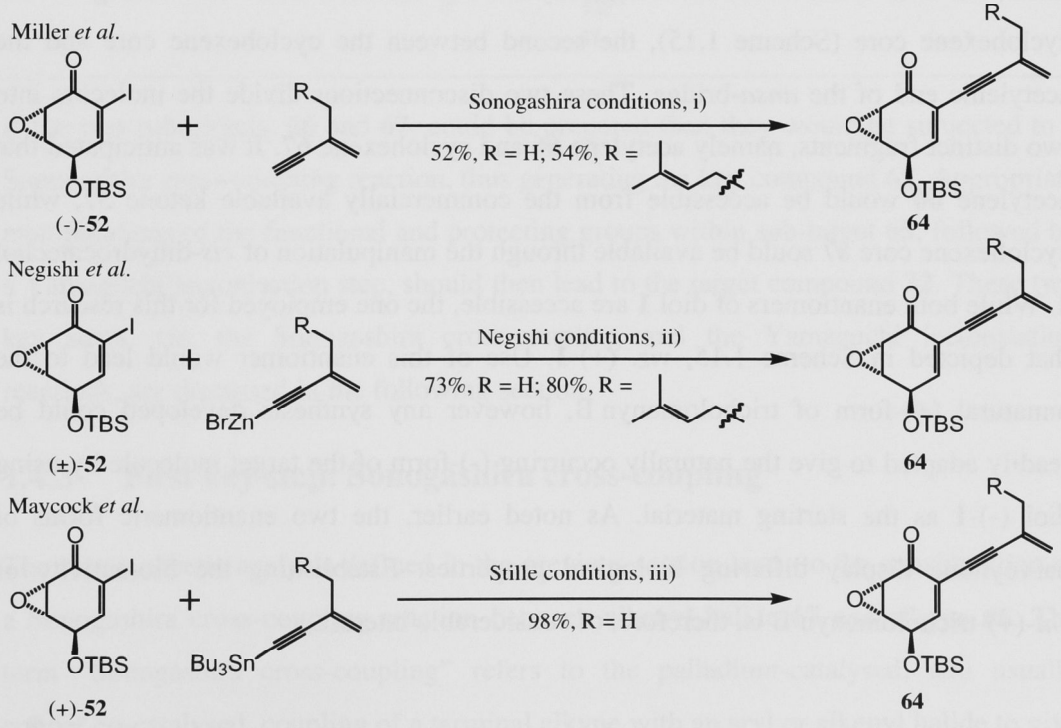
***Scheme 1.13**: Miller, Tachihara and Maycock preparations of epoxy-eneone **51**, a key compound in the synthesis of tricholomenyn A and harveynone*



Reagents and Conditions: i) a) Br_2 then $NaBH_4$, 62%; b) Ac_2O, NEt_3, DMAP, 72%; c) Amano PS-30 lipase, 26% [+ 47% other enantiomer]; d) Ti(O*i*-Pr)$_4$, 92%; ii) a) TBDMSOTf, NEt_3, 45%; b) CF_3CO_3H, Na_2HPO_4, 84%; iii) a) Zn, MeOH, 81%; b) PCC, 82%; iv) a) Dry Bakers Yeast, 74%, >98.4% ee; b) LiOH, MeOH/H_2O; c) Ac_2O, pyridine, 87% (over two steps); v) a) IBDA, I_2, CCl_4, *hν*, 91%; b) DBU, PhMe; c) K_2CO_3, MeOH, 78% (over two steps); d) TBDMSCl, imidazole, DMF, 98%; e) PPTS, H_2O/acetone, 90%; vi) a) H_2O_2, TritonB, THF, 80%; b) LiHMDS, THF, TMSCl, then PhSeCl, DCM; c) 35% H_2O_2, $NaHCO_3$, THF, 68% (over two steps); vii) a) acetone, dry HCl, 89%; b) Ac_2O, pyridine, 92%; c) $LiAlH_4$, Et_2O then $NaIO_4$, H_2O, 5 < pH < 6, 91%; d) TBDMSCl, imidazole, DMF, 35 °C, 98%; viii) 0.5 M NaOH, THF, 0 °C, 41%; ix) a) 30% H_2O_2, Triton B, THF, 0 °C, 89%; b) Ac_2O, *i*-Pr_2NEt, DMAP, DCM, 0 °C, 88%.

Each of these researchers then converted epoxide **51** into the corresponding α-iodoenone **52** using the protocol established in the Ogasawara synthesis (Scheme 1.12, on page 17). With the latter compound in hand, the pivotal palladium-mediated cross-coupling reaction followed (Scheme 1.14). For this reaction, Miller *et al.* developed a specific set of Sonogashira cross-coupling conditions tailored for use with cyclic α-iodo enones.[28] The yields obtained were in the low 50% range, however given that both Taylor and Ogasawara report being unable to achieve this reaction, Miller's results represent a considerable success. In Negishi's synthesis, the cross-coupling was (naturally!) performed using the reaction conditions bearing his name.[30] Thus, alkenyl iodide **52** was reacted with the zinc bromide derivative of the alkyne coupling partner, to give the cross-coupled product **64** in 73 – 80%. In the Maycock synthesis, the cross-coupling was carried out using Stille conditions and a high yield was reported for this reaction.[33]

***Scheme 1.14**: Palladium-mediated cross-coupling reactions used in the Miller, Negishi and Maycock syntheses of tricholomenyn A and harveynone*



Reagents and Conditions: i) $PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, THF, 0 °C; ii) $Pd(dba)_2$, trifurylphosphine, DMF, 18 °C; iii) $PdCl_2(PPh_3)_2$, CuI, $AsPh_3$, THF, 18 °C.

The differing cross-coupling procedures discussed above all serve to highlight that there is a range of conditions that can be used to link the two substructures of the target

compound. While the Sonogashira protocol has the advantage of not requiring derivatisation of the alkyne coupling partner, there are situations in which other protocols are more effective.

1.4 Thesis Aims and a Retrosynthetic Analysis of Tricholomenyn B

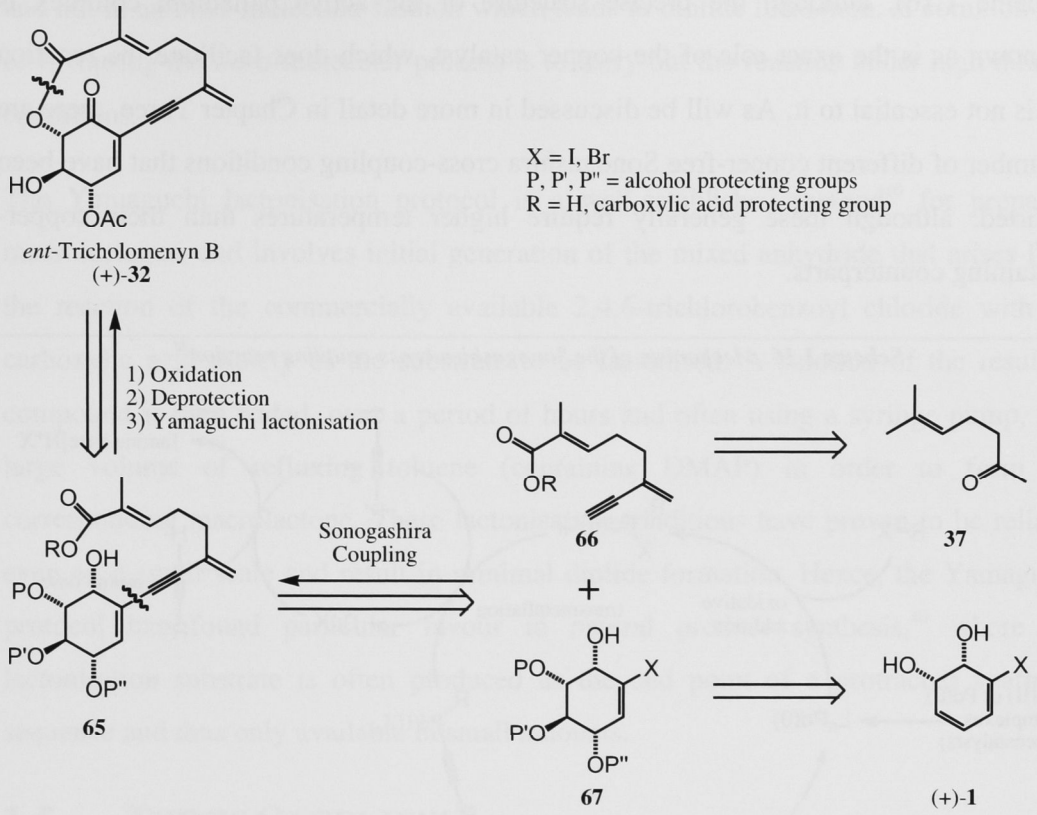
1.4.1 Aims

The work described in this thesis was directed towards the development of a synthesis of tricholomenyn B using enzymatically-derived *cis*-dihydrocatechols **1** as starting materials.

1.4.2 Retrosynthetic analysis

A retrosynthetic analysis of tricholomenyn B reveals two key disconnections that can be made, the first at the lactone functionality linking one end of the *ansa* bridge to the cyclohexene core (Scheme 1.15), the second between the cyclohexene core and the acetylenic end of the *ansa*-bridge. These two disconnections divide the molecule into two distinct fragments, namely acetylene **66** and cyclohexene **67**. It was anticipated that acetylene **66** would be accessible from the commercially available ketone **37**, while cyclohexene core **67** sould be available through the manipulation of *cis*-dihydrocatechol **1**. While both enantiomers of diol **1** are accessible, the one employed for this research is that depicted in Scheme 1.15, *viz.* (+)-**1**. Use of this enantiomer would lead to the unnatural (+)-form of tricholomenyn B, however any synthesis developed could be readily adapted to give the naturally occurring (-)-form of the target molecule by using diol (-)-**1** as the starting material. As noted earlier, the two enantiomeric forms of harveynone display differing biological properties. Establishing the bio-activity of *ent*-(+)-tricholomenyn B is, therefore, of considerable interest.

***Scheme 1.15**: Retrosynthetic analysis of* ent-(+)-*tricholomenyn B*



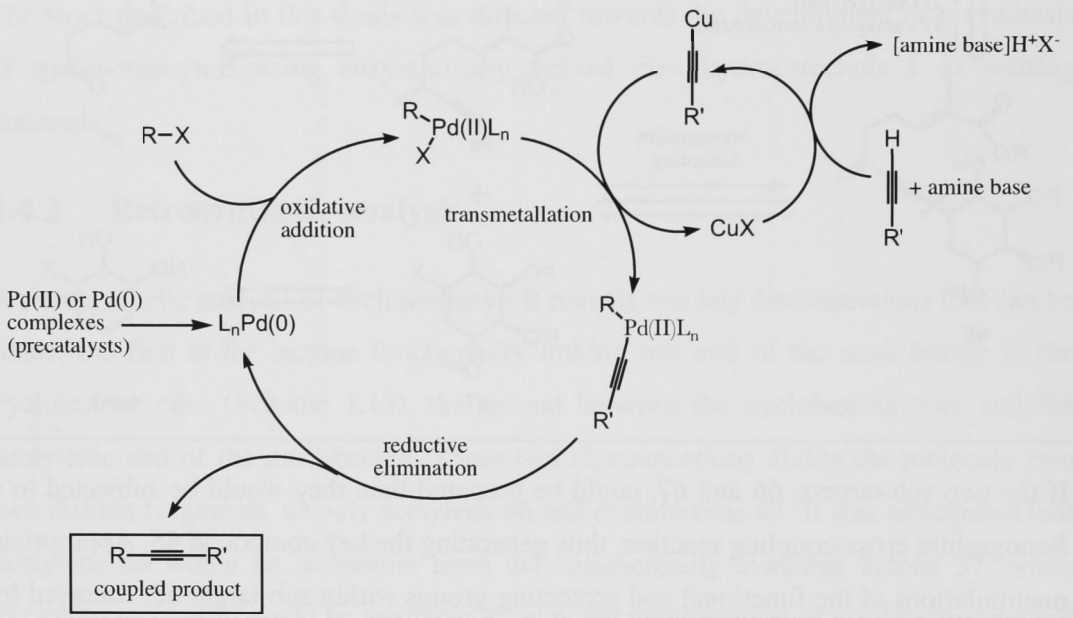
If the two sub-targets, **66** and **67**, could be prepared then they would be subjected to a Sonogashira cross-coupling reaction, thus generating the key compound **65**. Appropriate manipulations of the functional and protecting groups within sub-target **65**, followed by a Yamaguchi lactonisation step, should then lead to the target compound **32**. These two key steps, *viz.* the Sonogashira cross-coupling and the Yamaguchi lactonisation reactions, are discussed in the following section.

1.4.3 First key step: Sonogashira cross-coupling

The retrosynthetic analysis defined in the previous section leads to the consideration of a Sonogashira cross-coupling reaction between alkenyl halide **67** and alkyne **66**. The term "Sonogashira cross-coupling" refers to the palladium-catalysed, and usually copper co-catalysed, coupling of a terminal alkyne with an aryl or alkenyl halide to give an enyne.[38] This reaction has the advantage of being extremely functional group tolerant and can be conducted under mild conditions, often at or below room temperature. The order of reactivity of organic halides in Sonogashira cross-coupling reactions is I ≈ OTf > Br >> Cl, with alkenyl halides being more reactive than aryl halides.[39] The

reaction most likely follows an oxidative addition/reductive elimination pathway (Scheme 1.16), although the precise structure of the active palladium complex is unknown as is the exact role of the copper catalyst, which does facilitate the reaction but is not essential to it. As will be discussed in more detail in Chapter Three, there are a number of different copper-free Sonogashira cross-coupling conditions that have been reported, although these generally require higher temperatures than their copper-containing counterparts.

***Scheme 1.16**: Mechanism of the Sonogashira cross-coupling reaction*[38]



1.4.4 Second key step: Yamaguchi lactonisation

Besides the Sonogashira cross-coupling, the second key step being contemplated in the projected synthesis of (+)-tricholomenyn B is a Yamaguchi lactonisation reaction. The role of macrolactone forming reactions in natural product synthesis has recently been reviewed in a comprehensive manner.[40] Lactone moieties tend to be reactive, especially under basic conditions and, for this reason, it is common practice to assemble such moieties towards the end of a synthesis and from the corresponding *seco*-acid. Two distinct concerns arise in considering the use of a lactonisation reaction. The first is that the reaction will not normally proceed without some form of activation of the starting material. This is generally achieved by transforming either hydroxyl residue (i.e. the OH of the acid or alcohol) into a good leaving group. The second issue is the need to ensure

that the reaction proceeds in an *intra*-molecular fashion leading to the macrolactone, and not in an *inter*-molecular fashion which leads to diolide formation. A common way of favouring the *intra*-molecular process is to carry out the reaction under high dilution conditions.

The Yamaguchi lactonisation protocol is a well-established method[40] for preparing macrolactones, and involves initial generation of the mixed anhydride that arises from the reaction of the commercially available 2,4,6-trichlorobenzoyl chloride with the carboxylic acid moiety of the substrate to be lactonised. A solution of the resulting compound is then added, over a period of hours and often using a syringe pump, to a large volume of refluxing toluene (containing DMAP) in order to form the corresponding macrolactone. These lactonisation conditions have proven to be reliable even on a small scale and result in minimal diolide formation. Hence, the Yamaguchi protocol has found particular favour in natural product synthesis,[40] where the lactonisation substrate is often produced as the end point of a protracted synthetic sequence and thus only available in small amounts.

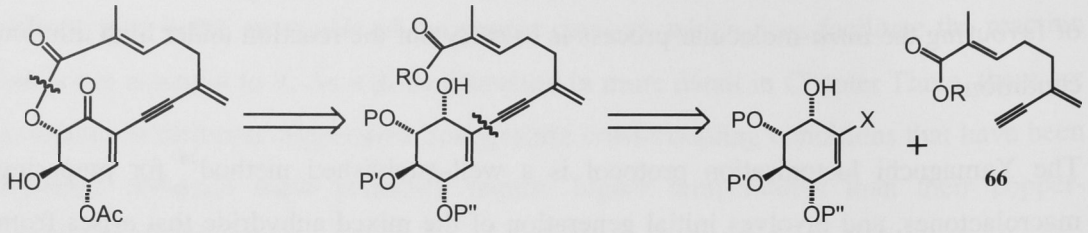
1.5 THESIS OVERVIEW

In Chapter Two, the synthesis of the *ansa* bridge-containing acetylenic sub-target **66** is detailed, as are some preliminary studies directed towards the synthesis of the *Z*-isomer of this compound. The outcomes of Sonogashira cross-coupling model studies involving sub-target **66** and iodobenzene as a substrate are also described.

The various routes explored in the preparation of the cyclohexene core-containing sub-target **67** are described in Chapter Three, along with investigations into the Sonogashira cross-coupling reaction between core **67** and alkyne **66** that leads to key compound **82**.

Chapter Four details the synthetic work carried out on compound **65** leading towards the completion of the synthesis of (+)-tricholomenyn B and lays out the difficulties experienced. Possible solutions that could lead to the completion of the synthesis of (+)-tricholomenyn B are discussed.

***Scheme 1.17**: Summary of the retrosynthetic analysis of (+)-tricholomenyn B employed in the present study*

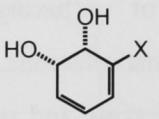


(+)-Tricholomenyn B
(+)-**32**

65

67

66



(+)-**1**

X = I, Br
P, P', P'' = alcohol protecting groups
R = H, carboxylic acid protecting group

1.6 REFERENCES

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PREPARATION OF THE *ANSA* BRIDGE-CONTAINING PORTION OF (+)-TRICHOLOMENYN B

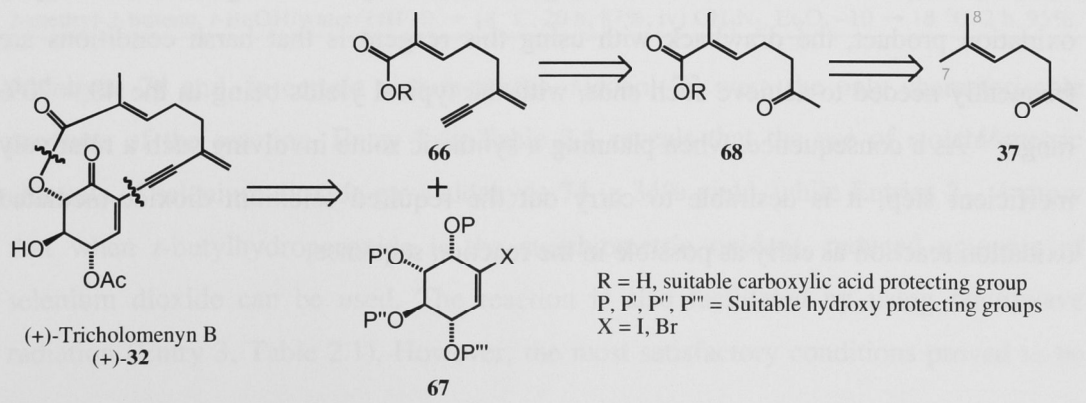
This chapter describes the synthesis of the carbon framework associated with the ansa *bridge of (+)-tricholomenyn B. Some preliminary studies directed towards the synthesis of the Z-analogue of the* ansa *bridge are described, as are the outcomes of Sonogashira cross-coupling studies carried out with the E isomer of the* ansa *bridge-containing compound.*

2.1 INTRODUCTION

2.1.1 Retrosynthetic analysis

As has been discussed in Chapter One, the retrosynthetic analysis of the target compound, (+)-tricholomenyn B, being employed in the present study divides the molecule into two sub-targets. One of these sub-targets, **66**, represents the carbon framework of the *ansa* bridge and the other, **67**, the cyclohexene core (Scheme 2.1). This chapter describes (successful) efforts to prepare the former sub-structure.

***Scheme 2.1**: Retrosynthetic analysis*



In the forward or synthetic sense and beginning with the commercially available ketone **37**, the first challenge in making the *ansa*-bridging fragment of final target (+)-**32** is to selectively oxidise the C7 methyl group (within compound **37**) whilst leaving its C8-counterpart untouched. With a suitable acid or ester moiety installed, the next task would be to selectively form the kinetic enolate from ketone **68**. Trapping of this enolate as the triflate would then provide a suitable partner for Sonogashira cross-coupling with trimethylsilyl acetylene and thereby complete the assembly of the *ansa*-bridging fragment **68**.

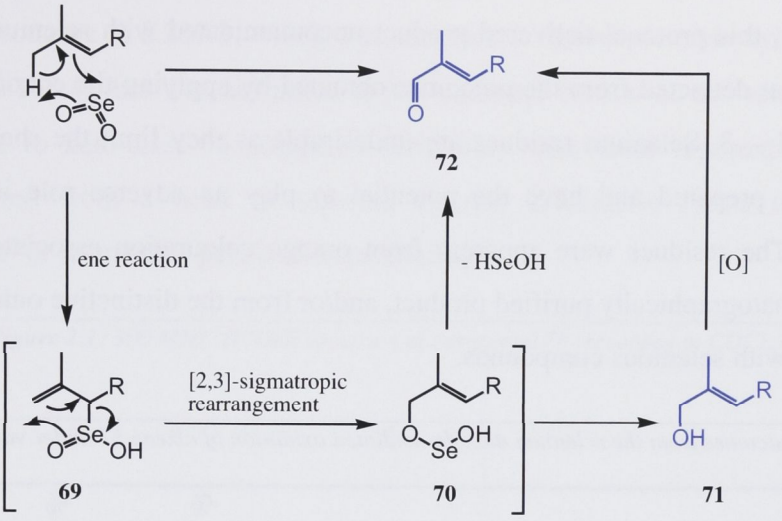
2.2 SYNTHESIS OF KETO-COMPOUND 68

2.2.1 Selenium dioxide: a reagent for the *E*-selective oxidation of allylic methyl groups

In considering the challenge of selectively oxidising C7 of compound **37**, selenium dioxide appeared to be the reagent of choice. Indeed, oxidation of *gem*-dimethylated trisubstituted alkenes such as **37** by this reagent has been shown to proceed in a highly *E*-selective manner.[1] The reaction probably involves an initial ene reaction to give species **69**, which undergoes a [2,3]-sigmatropic rearrangement to deliver intermediate compound **70** (Scheme 2.2). Species **70** can then undergo Se-O cleavage *via* a pathway that has yet to be conclusively established, but could lead to either aldehyde **72** or alcohol **71**. Alcohol **71** is then able to undergo further oxidation to the corresponding aldehyde.[2] Selenium dioxide can either be employed stoichiometrically or in near catalytic amounts when used in conjunction with a co-oxidant such as *t*-butylhydroperoxide.

While selenium dioxide offers the advantage of selectively delivering the desired allylic oxidation product, the drawback with using this reagent is that harsh conditions are frequently needed to achieve such ends, with the typical yields being in the 40 – 70% range.[3,4] As a consequence, when planning a synthetic route involving such a relatively inefficient step, it is desirable to carry out the required selenium dioxide-mediated oxidation reaction as early as possible in the reaction sequence.

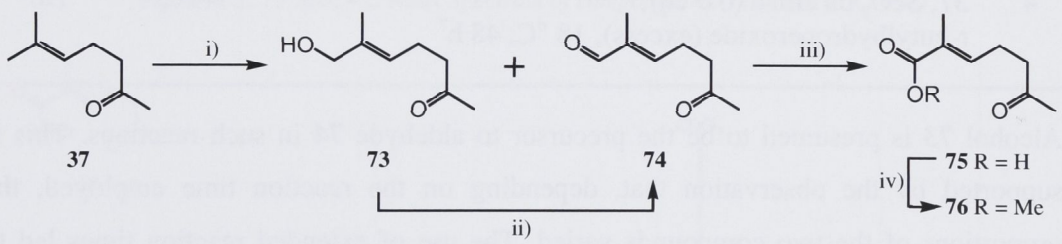
***Scheme 2.2**: Mechanistic origin of the* E*-selectivity observed in the selenium dioxide-mediated oxidation of alkenes incorporating terminal methyl groups*



2.2.2 Results and discussion

In pursuing the target keto-compound **68**, and particularly the methyl ester, **76**, (Scheme 2.3) the commercially available ketone **37** was subjected to reaction with selenium dioxide under a variety of conditions and the relevant outcomes are summarised in Table 2.1.

Scheme 2.3**: Preparation of compound **76



Reagents and Conditions: i) See Table 2.1; ii) MnO_2, Et_2O, 18 °C, 20 h, 61%; iii) $NaClO_2$, $NaH_2PO_4 \bullet H_2O$, 2-methyl-2-butene, *t*-BuOH/water/THF, 0 → 18 °C, 20 h, 87%; iv) CH_2N_2, Et_2O, –10 → 18 °C, 2 h, 95%.

Aldehyde **74** and, in certain circumstances, alcohol **73** were the only characterisable products of the reaction. Entry 1 in Table 2.1 reveals that the use of stoichiometric amounts of selenium dioxide gave aldehyde **74** in 34% yield, while Entries 2 – 4 show that when *t*-butylhydroperoxide is the stoichiometric oxidant, reduced amounts of selenium dioxide can be used. The reaction is also facilitated by using microwave radiation (Entry 3, Table 2.1). However, the most satisfactory conditions proved to be

those shown in Entry 4, in which the selenium dioxide is adsorbed onto silica gel prior to use. This afforded aldehyde **74** in a modest but acceptable yield of 49%. More importantly, this protocol delivered product uncontaminated with selenium residues, a situation that detracted from the outcomes obtained by applying the conditions defined in Entries 1 – 3. Selenium residues are undesirable as they limit the shelf life of any compounds prepared and have the potential to play an adverse role in subsequent reactions. The residues were apparent from orange colouration associated with even flash chromatographically purified product, and/or from the distinctive onion-like odour associated with selenious compounds.

***Table 2.1**: Outcomes from the selenium dioxide-mediated oxidation of alkene **37** under various conditions*

Entry	Conditions	% alcohol **73**	% aldehyde **74**	SeO_2 residues?
1	**37**, SeO_2 (1.2 eq), dioxane, EtOH, 80 °C, 4.5 h[4]	-	34	Yes
2	**37**, SeO_2 (0.1 eq), salicylic acid, *t*-butylhydroperoxide (excess), 18 °C, 65 h[5]	18	32	Yes
3	**37**, SeO_2 on silica (0.5 eq), *t*-butylhydroperoxide (excess), microwave, 150 W, 25 min[6]	-	48	Yes
4	**37**, SeO_2 on silica (0.5 eq), *t*-butylhydroperoxide (excess), 18 °C, 48 h[7]	-	49	No

Alcohol **73** is presumed to be the precursor to aldehyde **74** in such reactions. This is supported by the observation that, depending on the reaction time employed, the proportions of the two compounds varied. The use of extended reaction times led to more of aldehyde **74**. In situations where alcohol **73** was obtained, oxidation of the compound with manganese dioxide provided aldehyde **74**.

Having successfully prepared the desired aldehyde **74**, its conversion into the corresponding carboxylic acid **75** was then carried out using the so-called Pinnick oxidation conditions (Scheme 2.3, on the previous page).[8] Compound **75** was then converted into the previously reported methyl ester **76**[9,10] using diazomethane. The spectroscopic data acquired on compound **76** were in excellent agreement with those reported in the literature[9,10] and in accord with the assigned structure. In particular, the

^{1}H NMR spectrum of methyl ester **76** (Figure 2.1) showed a diagnostic singlet at δ 3.68 corresponding to the methyl ester functional group. The ^{13}C NMR spectrum (Figure 2.2) featured a resonance at δ 207.3, which was assigned to the ketone carbonyl carbon and another, at δ 168.4, that was attributed to the carbonyl carbon of the ester unit. The present route to keto-ester **76** compares favourably with those reported previously, which suffered from a need to separate *E*- and *Z*-isomeric forms of synthetic intermediates[9] or from other purification problems.[10]

***Figure 2.1**: 300 MHz ^{1}H NMR spectrum of compound **76** (recorded in $CDCl_3$)*

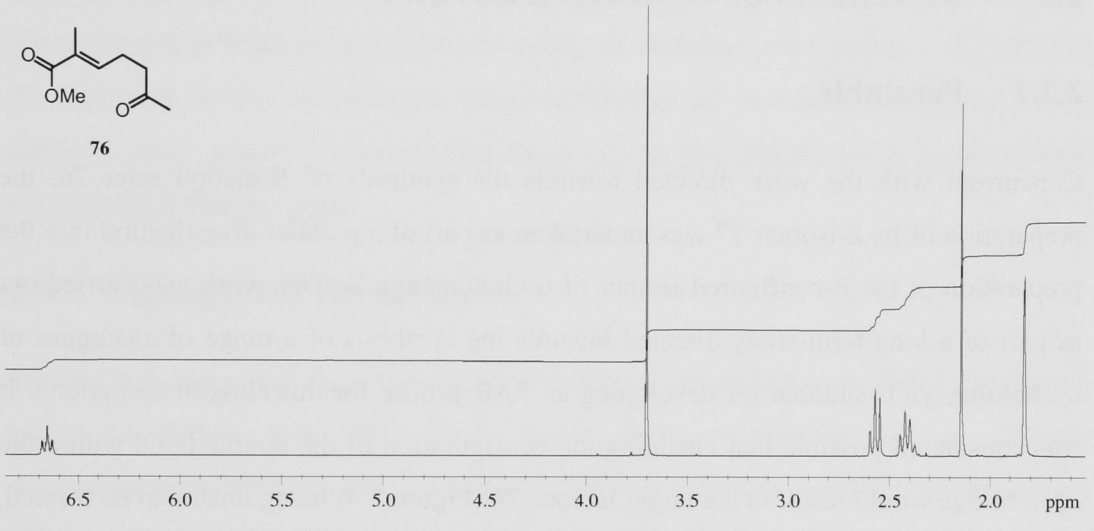
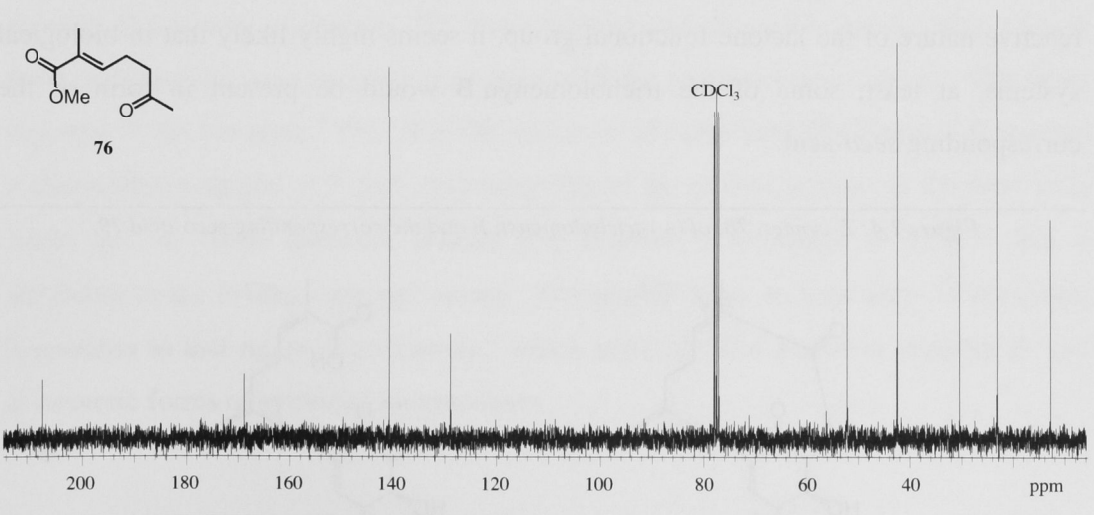


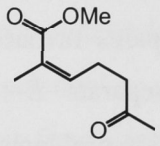
***Figure 2.2**: 75 MHz ^{13}C NMR Spectrum of compound **76** (recorded in $CDCl_3$)*



With *E*-methyl ester **76** in hand, the next sequence of events in the elaboration of this compound to the target molecule **66** involved the installation of the enyne moiety.

However, before discussing work directed towards such ends, the synthesis of the *Z*-isomer, **77** (Figure 2.3), of methyl ester **76** is described below.

Figure 2.3: Z-methyl ester 77



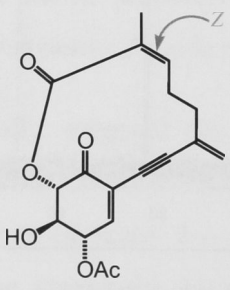
77

2.3 SYNTHESIS OF Z-METHYL ESTER 77

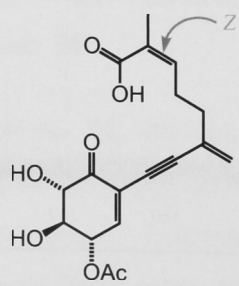
2.3.1 Preamble

Concurrent with the work directed towards the synthesis of *E*-methyl ester **76**, the preparation of its *Z*-isomer **77** was undertaken as part of a parallel investigation into the preparation of the *Z*-configured isomer of tricholomenyn B. This work was carried out as part of a long-term study directed towards the synthesis of a range of analogues of tricholomenyn B suitable for developing an SAR profile for this class of compound. It was considered possible that changing the configuration of the double bond within the *ansa* bridge would result in the target lactone **78** (Figure 2.4) being unable to be formed, although this is not necessarily problematic as the *seco* acid* of tricholomenyn B itself as well as related compounds could still be biologically active. Indeed, given the reactive nature of the lactone functional group, it seems highly likely that in biological systems, at least, some of the tricholomenyn B would be present in form of the corresponding *seco*-acid.

Figure 2.4**: Z-isomer, **78**, of (+)-tricholomenyn B and the corresponding* seco*-acid **79



78



79

* *Seco* acid is a term used to describe the hydrolysed, acyclic form of a lactone.

While a different approach was undertaken in the preparation of the *Z*-methyl ester **77** as compared to that employed in the synthesis of isomer **76**, it was anticipated that incorporation of the former unit into the carbon framework of the target compound **78** would be carried out using a sequence of events analogous to that planned for *E*-methyl ester **76**.

2.3.2 Differing approaches to control of double bond geometry

In the synthesis of compound **76**, control of the geometry of the double bond was achieved through the use of an oxidising agent (selenium dioxide) mechanistically constrained to give the desired stereochemistry. In contrast, in the sequence described in the following section, control was achieved through the geometric constraints of the substrate itself, which determined that the newly formed alkenyl bond would possess the targeted *Z*-configuration.

2.3.3 Results and discussion

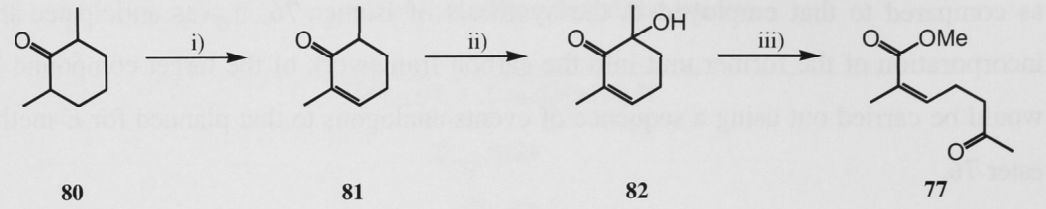
Starting with the commercially available 2,6-dimethylcyclohexanone (**80**),* the alkenyl bond associated with the final target was introduced *via* a one-pot bromination/dehydrobromination reaction[11] (Scheme 2.4). The resulting cyclohexenone (**81**) was then α-hydroxylated using the Davis oxaziridine† and the ensuing α'-hydroxy ketone **82** subjected to oxidative cleavage using lead tetraacetate in methanol.[13] In this manner, the known compound **77**[9] was obtained and the spectroscopic data derived from this material were in good agreement with the proposed structure and with those reported in the literature.[9] The ^{1}H NMR spectrum of compound **77** (Figure 2.5) showed a characteristic singlet at δ 3.61, corresponding to the methyl protons of the ester unit, while the ^{13}C NMR spectrum (Figure 2.6) featured a resonance at δ 207.6 that is attributed to the ketone carbonyl moiety. The present route to keto-ester **77** compares favourably to that reported previously,[9] which suffered from a need to separate *E*- and *Z*-isomeric forms of synthetic intermediates.

---

* Compound **80** was supplied as a 1:1 mixture of *cis*- and *trans*-isomers.

† Systematic name: 3-phenyl-2-phenylsulfonyl oxaziridine. This α-hydroxylating reagent was developed by the group of Davis [12].

Scheme 2.4**: Synthesis of compound **82



80 **81** **82** **77**

Reagents and Conditions: i) NBS, AIBN, $ClCH_2CH_2Cl$, reflux, 4.75 h, 60%; ii) KHMDS then 3-phenyl-2-phenylsulfonyl oxaziridine, THF, –78 °C, 1 h, 66%; iii) $Pb(OAc)_4$, MeOH, 40 °C, 3 h, 84%.

***Figure 2.5**: 300 MHz ^1H NMR spectrum of compound **77** (recorded in $CDCl_3$)*

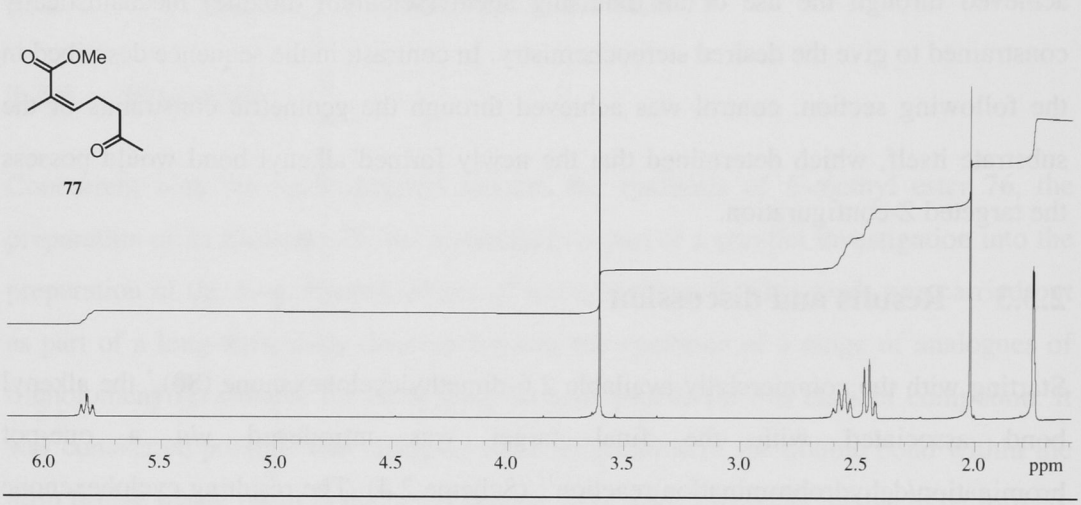
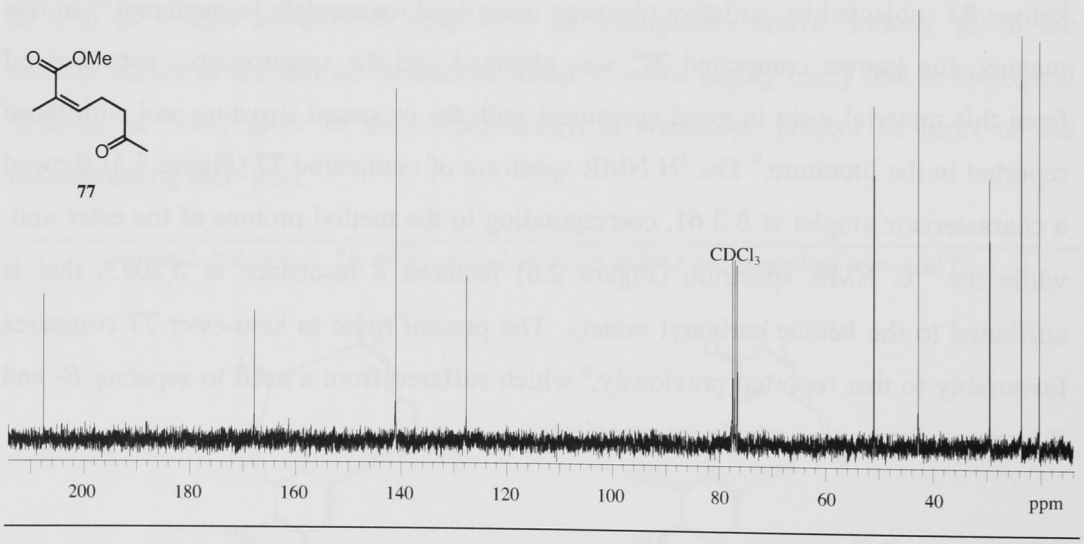


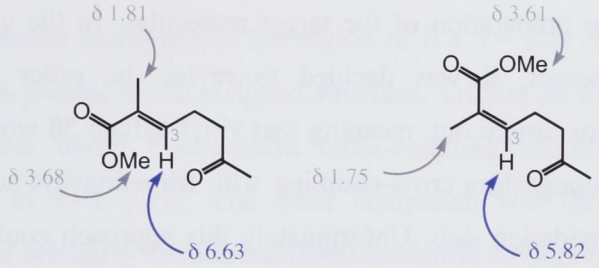
***Figure 2.6**: 75 MHz ^{13}C NMR spectrum of compound **77** (recorded in $CDCl_3$)*



Compound **77** is the geometric isomer of keto-ester **76**, the synthesis of which has been detailed earlier in this chapter. A comparison of the key resonances observed in the ^1H NMR spectra of both compounds **77** and **76** is shown in Figure 2.7 and this reveals that

in the former system the signal due to the alkenyl proton (H3) appears at δ 5.82, whilst in isomer **76** the corresponding resonance is observed at δ 6.63. This difference presumably reflects the de-shielding effect exerted by the carbomethoxy group on the *cis*-related alkenyl proton in the latter system.

Figure 2.7**: A comparison of selected ^{1}H NMR spectral resonances observed for isomers **76** and **77

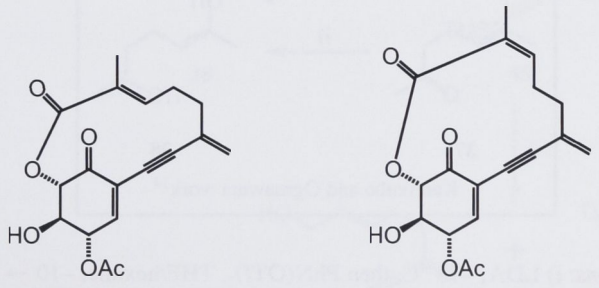


76 **77**

2.4 Attempted Elaboration of Methyl Esters 76 and 77 to the Target *Ansa* Bridge-containing Compounds

Having successfully prepared both *E*-methyl ester **76** and its congener **77**, the next task was the continued elaboration of these compounds so as to establish the complete carbon skeleta associated with the *ansa* bridges of the corresponding final targets, namely (+)-**32** and its *Z*-isomer **78**.

Figure 2.8**: Final targets (+)-**32** and its Z-isomer **78



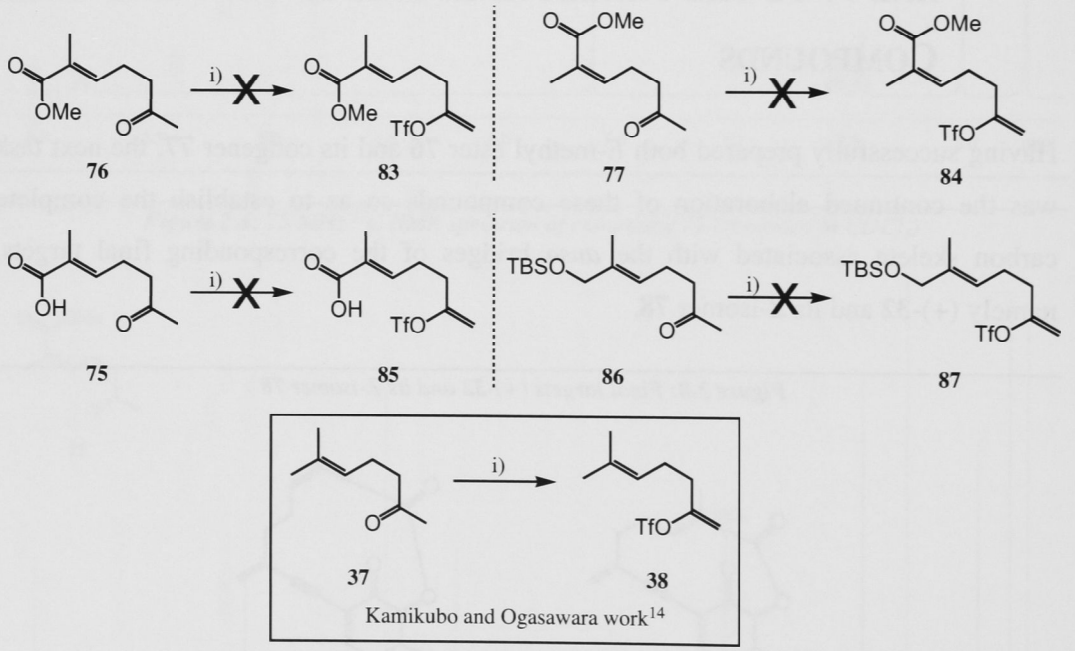
(+)-Tricholomenyn B
(+)-**32**

78

Accordingly, attention was turned to generating vinyl triflate **83** from ketone **76** (Scheme 2.5) using the procedure detailed by Kamikubo and Ogasawara[14] in which the kinetic enolate obtained by treating ketone **37** with LDA was trapped using

N-phenyl-*bis*-triflimide to give triflate **38**. Unfortunately, when methyl ester **76** was subjected to these conditions, a quantitative recovery of the starting material was observed. Such an outcome was also encountered when methyl ester **77** was subjected to the same conditions. Attempts to generate vinyl triflate **85** from carboxylic acid **75** were equally unsuccessful, as were attempts to prepare triflate **87** from *t*-butyldimethylsilyl ether **86**.* It was concluded from these results that this approach was unsuited to the preparation of the target molecules. In the case of the sequence involving the *E*-isomer, it was decided to revise the order in which chemical transformations were carried out, meaning that vinyl triflate **38** would be prepared first and subjected to Sonogashira cross-coupling with trimethylsilyl acetylene prior to the selenium dioxide oxidation step. Unfortunately this approach could not be adapted to the preparation of the corresponding *Z*-isomer and, so, attempts to prepare the *Z*-isomer of (+)-tricholomenyn B were discontinued.

Scheme 2.5**: Unsuccessful attempts to form triflates **83**, **84**, **85** and **87



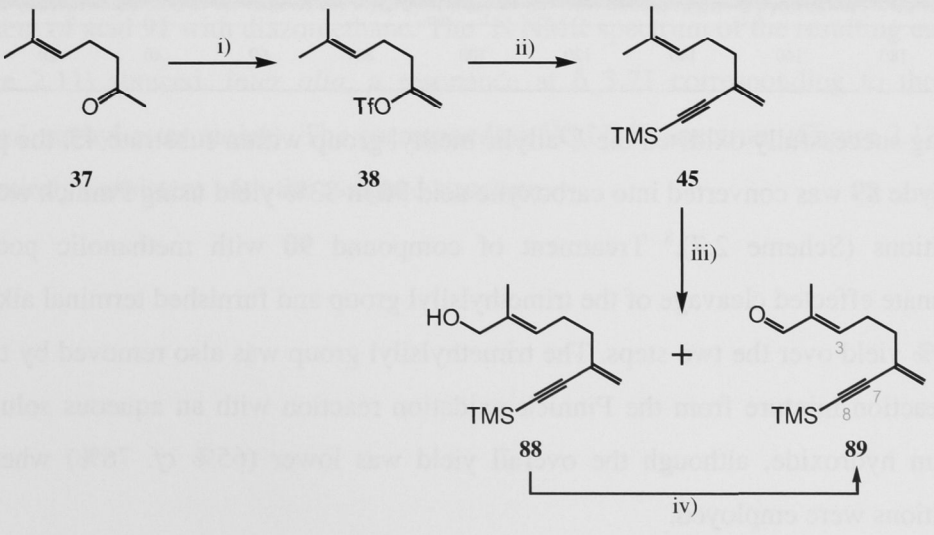
Reagents and Conditions: i) LDA, –78 °C, then $PhN(OTf)_2$, THF/hexane, –10 → 18 °C, 16 h.

* Compound **86** was prepared from alcohol **73** by protecting the alcohol moiety as a *t*-butyldimethylsilyl ether under standard conditions [15].

2.5 REVISED APPROACH TO THE SYNTHESIS OF *ANSA* BRIDGE-CONTAINING COMPOUND 66

In accord with the revised plan discussed in the preceding section, ketone **37** was treated with LDA and the resulting enolate trapped using *N*-phenyl-*bis*-triflimide to furnish the known triflate **38**[14] in 73% yield (Scheme 2.6). The ^{1}H NMR spectrum of compound **38** showed three one-proton multiplets in the region of δ 4.5 – 5.5, corresponding to the three alkenic protons present in the assigned structure. Triflate **38** was then treated with trimethylsilylacetylene under Sonogashira cross-coupling conditions[16] to give the known enyne **45**[14] in 97% yield. The latter compound was then subjected to the previously optimised selenium dioxide-mediated oxidation conditions and so afforded a chromatographically separable mixture of alcohol **88** (20% yield) and aldehyde **89** (32% yield). Alcohol **88** was subsequently oxidised to aldehyde **89** using manganese dioxide. The ^{1}H NMR spectrum of compound **89** (Figure 2.9) showed a one-proton singlet at δ 9.39 that was attributed to the aldehydic proton. A triplet of quartets observed at δ 6.47 was assigned to the alkenyl proton (H3) while the two resonances present in the corresponding ^{13}C NMR spectrum at δ 104.6 and 94.9 (Figure 2.10) were attributed to the two alkynyl carbons, C7 and C8 within compound **89**. The IR spectrum displayed a weak C≡C stretching band at 2144 cm^{-1}.

Scheme 2.6**: Synthesis of aldehyde **89** as part of a revised approach to sub-target **66



Reagents and Conditions: i) LDA, –78 °C, 1 h, then $PhN(OTf)_2$, THF/hexane, –78 → 18 °C, 20 h, 73%; ii) TMS-acetylene, $PdCl_2(CH_3CN)_2$, CuI, piperidine/THF, 18 °C, 0.6 h, 97%; iii) SeO_2 on silica, *t*-BuOOH, DCM/nonane, 18 °C, 72 h, 20% **88**, 32% **89**; iv) MnO_2, Et_2O, 18 °C, 22 h, 66%.

***Figure 2.9**: 300 MHz ^{1}H NMR spectrum of aldehyde **89** (recorded in $CDCl_3$)*

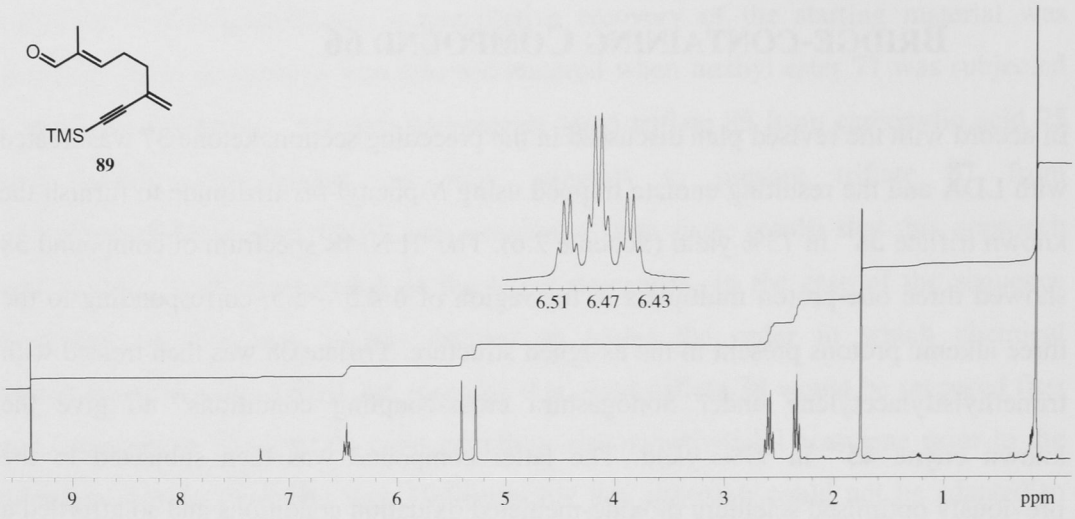
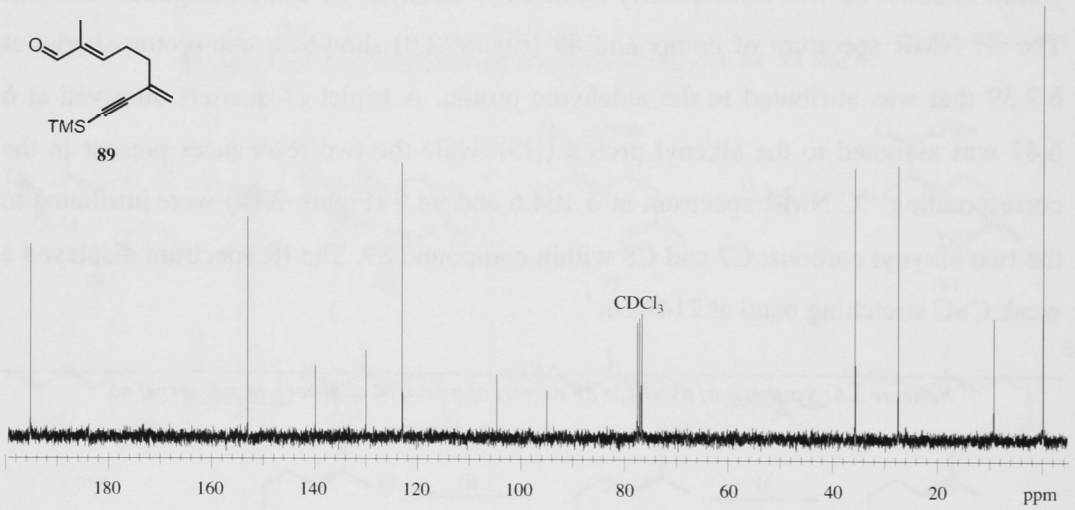
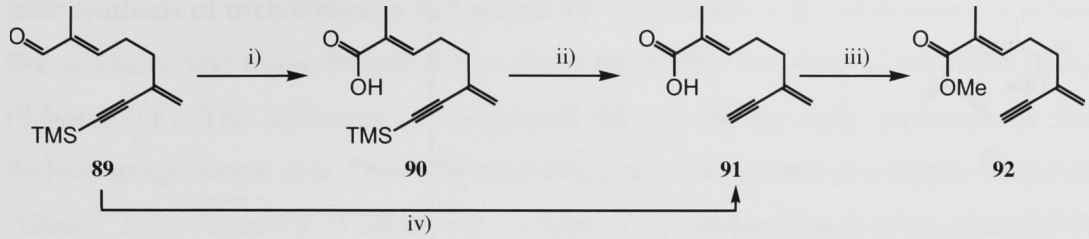


***Figure 2.10**: 75 MHz ^{13}C NMR spectrum of aldehyde **89** (recorded in $CDCl_3$)*



Having successfully oxidised the *E*-allylic methyl group within substrate **45**, the product aldehyde **89** was converted into carboxylic acid **90** in 83% yield using Pinnick oxidation conditions (Scheme 2.7).[8] Treatment of compound **90** with methanolic potassium carbonate effected cleavage of the trimethylsilyl group and furnished terminal alkyne **91** in 76% yield over the two steps. The trimethylsilyl group was also removed by treating the reaction mixture from the Pinnick oxidation reaction with an aqueous solution of sodium hydroxide, although the overall yield was lower (65% *cf.* 76%) when such conditions were employed.

Scheme 2.7**: Completion of the synthesis of* ansa *bridge-containing compound **92



Reagents and Conditions: i) $NaClO_2$, $NaH_2PO_4 \bullet H_2O$, 2-methyl-2-butene, *t*-BuOH/water/THF, 0 → 18 °C, 20 h, 83%; ii) K_2CO_3, MeOH, 18 °C, 16 h, 92%; iii) CH_2N_2, Et_2O, –10 °C, 95%; iv) $NaClO_2$, $NaH_2PO_4 \bullet H_2O$, 2-methyl-2-butene, *t*-BuOH/water/THF, 0 → 18 °C, 20 h, basic work-up, 65%.

The ^{1}H NMR spectrum of compound **91** displayed a one-proton singlet at δ 2.92 that was attributed to the terminal alkynyl proton while the IR spectrum featured a characteristically sharp ≡C-H stretching band at 3295 cm^{-1}. The broad band observed at 2931 cm^{-1} in the same spectrum is attributed to the O-H stretch of the carboxylic acid residue. The assigned structure was also supported by the EI mass spectrum, which showed a molecular ion at *m/z* 164 and an accurate mass measurement on this species established that it was of the expected composition, namely $C_{10}H_{12}O_2$.

The acquisition of compound **91** represented a significant milestone, as it was one of the two coupling partners sought for participation in the Sonogashira cross-coupling destined to join the two hemispheres of (+)-tricholomenyn B. However, it was considered a possibility that the free carboxylic acid moiety could interfere with this cross-coupling reaction, so the corresponding methyl ester **92** was also prepared by treatment of acid **91** with diazomethane. The ^{1}H NMR spectrum of the resulting ester **92** (Figure 2.11) showed, *inter alia*, a resonance at δ 3.71 corresponding to the just-installed methyl ester moiety. The corresponding ^{13}C NMR spectrum (Figure 2.12) was also entirely consistent with the assigned structure.

***Figure 2.11**: 300 MHz ^{1}H NMR spectrum of compound **92** (recorded in $CDCl_3$)*

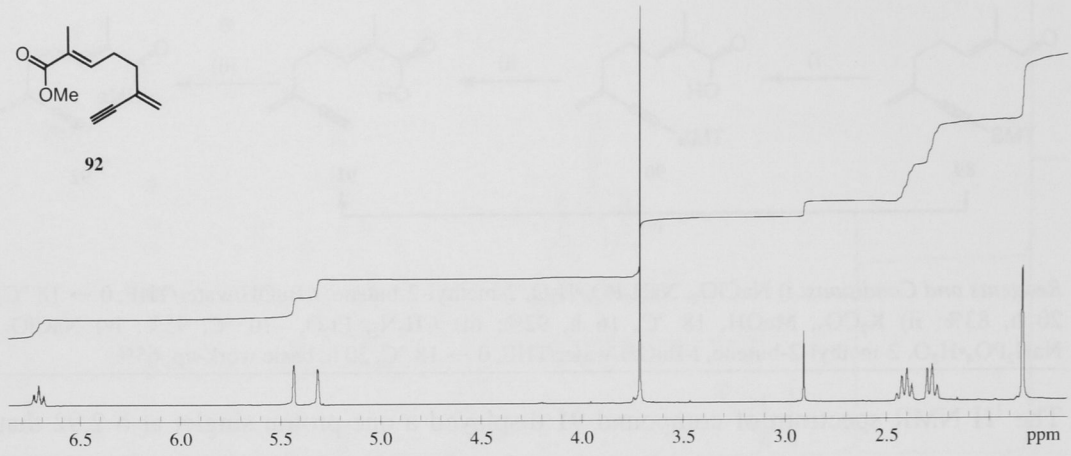
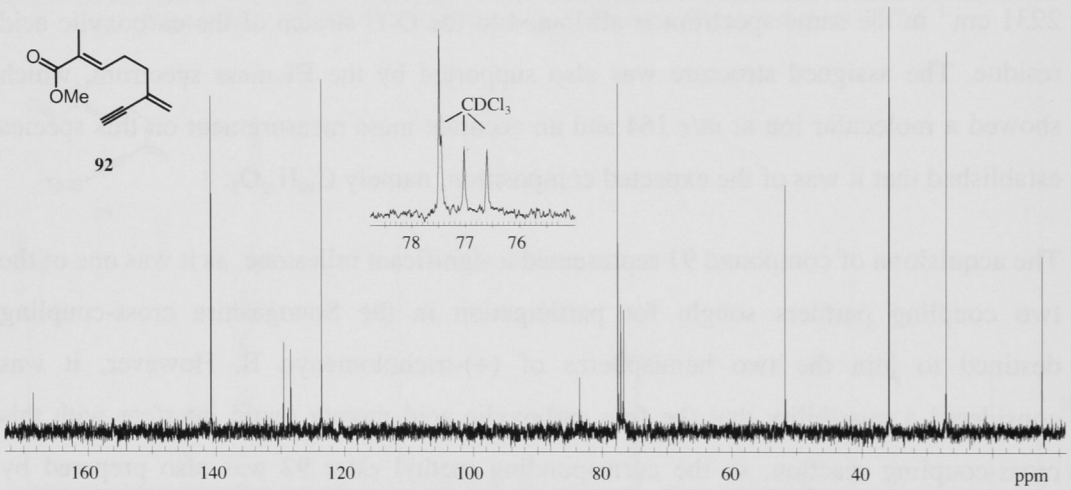


***Figure 2.12**: 75 MHz ^{13}C NMR spectrum of compound **92** (recorded in $CDCl_3$)*

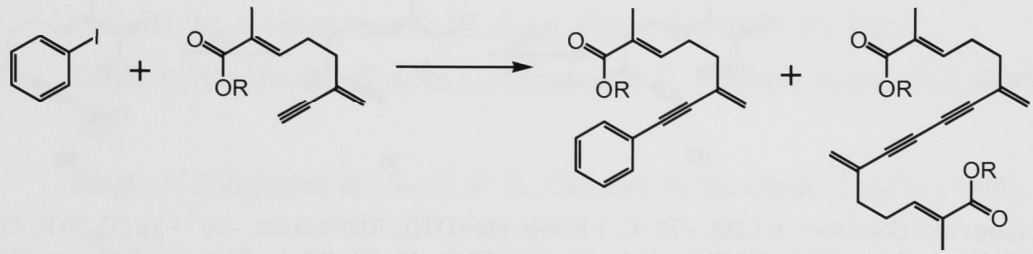


2.6 Model Studies Related to the Pivotal Sonogashira Cross-coupling Reaction

Having successfully prepared the *ansa* bridge-containing portion of (+)-tricholomenyn B, some preliminary investigations were undertaken in order to establish the capacity of carboxylic acid **91** and/or methyl ester **92** to engage in Sonogashira cross-coupling reactions. In the studies described here, iodobenzene was selected as a simple and readily available model for the core of (+)-tricholomenyn B. Additionally, as aryl halides are generally less reactive Sonogashira cross-coupling partners than alkenyl halides,[17] using iodobenzene as the model halide was unlikely to create false expectations regarding the reactivity of the real system, *viz.* alkenyl halide

67. Using the conditions developed by Miller *et al.* during the course of establishing their synthesis of tricholomenyn A,[18] alkyne **92** was coupled with iodobenzene to afford two products, aryl enyne **94** and alkyne dimer **96**, in 38% and 46% yields respectively (Scheme 2.8). The structures of compounds **94** and **96** are fully supported by the derived spectroscopic data. Dimer **96** most likely arises as a result of a copper-mediated "Glaser" homo-coupling of alkyne **92** – a type of by-product that is often observed in Sonogashira cross-coupling reactions.[19] When carboxylic acid **91** was subjected to the same conditions only starting material was recovered, thus suggesting that it is extremely important to avoid using substrates containing a free carboxylic acid moiety in these types of cross-coupling reactions.

***Scheme 2.8**: Sonogashira cross-coupling model studies*



91 R = H
92 R = Me

93 R = H
94 R = Me

95 R = H
96 R = Me

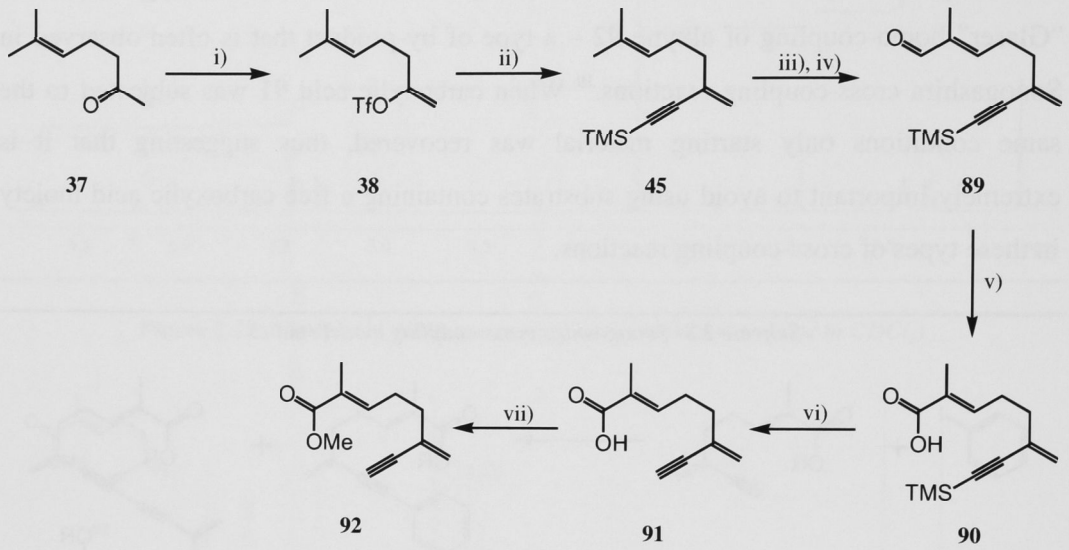
Reagents and Conditions: $PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, THF, 0 °C, 2.5 h; R = H, only starting material recovered; R = Me, 38% **94**, 46% **96**.

2.7 CONCLUSIONS

Stereoselective syntheses of the methyl esters, **76** and **82**, of (*E*)- and (*Z*)-2-methyl-6-oxohept-2-enoic have been achieved, and a paper detailing much of this work has been published.[20] Unfortunately, these compounds proved resistant to further elaboration in the desired manner. Accordingly, a revised sequence was pursued that involved delaying the selenium dioxide-mediated oxidation reaction by employing compound **45**, rather than congener **37**, as the substrate for this process. This allowed the synthesis of the desired *ansa* bridge-containing compound **92** to be achieved in six steps from commercially available ketone **37** (Scheme 2.9). Model studies related to the projected and pivotal Sonogashira cross-coupling reaction were carried out using iodobenzene and methyl ester **92** or carboxylic acid **91** as reaction partners. Such studies have established the need to mask the free carboxylic acid functionality to ensure an effective

outcome. Nevertheless, all available evidence suggests that the synthetic plan defined at the beginning of this Chapter is a valid one. Details of efforts to implement further elements of this plan are provided in the following Chapter.

Scheme 2.9**: Summary of the synthesis of* ansa *bridge-containing compound **92



Reagents and Conditions: i) LDA, –78 °C, 1 h, then $PhN(OTf)_2$, THF/hexane, –10 → 18 °C, 20 h, 73%; ii) TMS-acetylene, $PdCl_2(CH_3CN)_2$, CuI, piperidine/THF, 18 °C, 0.6 h, 97%; iii) SeO_2 on silica, *t*-BuOOH, DCM/nonane, 18 °C, 72 h, 32% **89**, 20% **88**; iv) **88**, MnO_2, Et_2O, 18 °C, 22 h, 66%; v) $NaClO_2$, $NaH_2PO_4 \bullet H_2O$, 2-methyl-2-butene, *t*-BuOH/water/THF, 0 → 18 °C, 20 h, 83%; vi) K_2CO_3, MeOH, 18 °C 16 h, 92%; vii) CH_2N_2, Et_2O, –10 °C, 1 h, 95%.

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PREPARATION OF THE CYCLOHEXENE PORTION OF (+)-TRICHOLOMENYN B

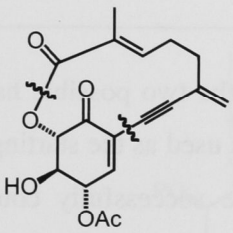
*This chapter describes the synthesis of the cyclohexene core, **67**, of (+)-tricholomenyn B. Three approaches utilising different protecting group regimes are discussed, as are issues associated with the use of the iodo- or bromo- forms of diol **1** as the starting material. Work carried out in developing a high-yielding Sonogashira cross-coupling procedure for linking alkenyl halide **67** and alkyne **92** is also described.*

3.1 INTRODUCTION

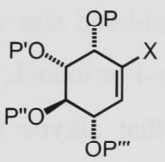
3.1.1 Retrosynthetic analysis recap

Having successfully synthesised the *ansa* bridge-containing portion, **92**, of (+)-tricholomenyn B, attention was next focussed on developing a suitable route to the corresponding cyclohexene core **67** (Figure 3.1).

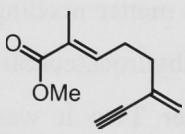
Figure 3.1**: (+)-Tricholomenyn B and the two synthetic sub-targets **67** and **92



(+)-Tricholomemyn B
(+)-**32**



67



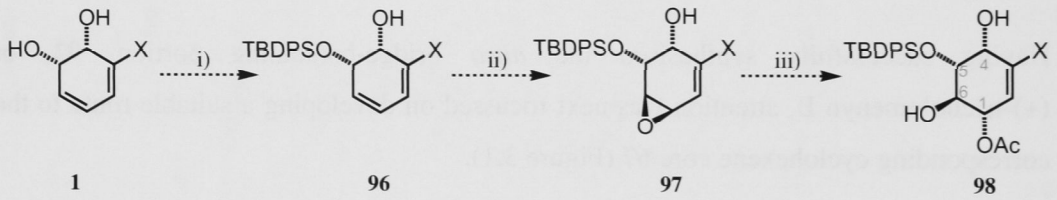
92

P, P', P", and P'''' = hydroxy protecting groups
X = I or Br

A major concern associated with developing a synthesis of this important sub-structure was the need to control the stereochemistry of any new functionality installed. Another important consideration was the need to use appropriate protecting groups for the hydroxy functionalities so as to facilitate the selective manipulation of these moieties.

Accordingly, a strategy was devised with these two issues in mind and which sought to exploit the very bulky nature of the *t*-butyldiphenylsilane (TBDPS) moiety as a hydroxy protecting group to ensure that regio-selective manipulation of the two hydroxyl groups within compound **1** could be achieved. In particular, the mono-protected *cis*-dihydrocatechol **96** was expected to undergo facially selective epoxidation to form compound **97** by virtue of the blocking effect of the TBDPS group (Scheme 3.1). This reaction would then be followed by a regio- and stereo-selective ring-opening process using acetate as the nucleophile and thus giving conduritol derivative **98**. Compound **98** not only embodies the desired *trans-trans* relationship between the substituents at C1, C6 and C5, but also possesses an acetate residue at the first of these positions, as is required for the preparation of (+)-tricholomenyn B. Additionally, of the two free hydroxy groups present in compound **98**, only one is in an allylic position (C4), meaning that it might be able to be selectively oxidised to the corresponding ketone, as is required for the preparation of the target compound (+)-**32**.

***Scheme 3.1**: Plan for the first approach to the synthesis of the cyclohexene core of (+)-tricholomenyn B*



Reagents: i) TBDPSCl, imidazole (mono-protection); ii) *m*-CPBA (epoxidation); iii) AcOH/NaOAc (ring opening).

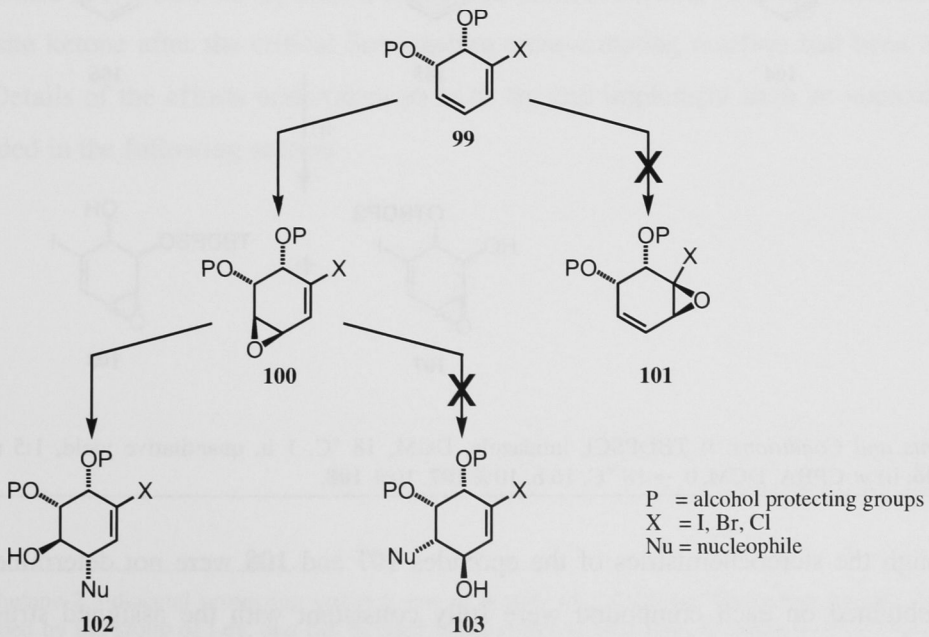
The final matter needing to be considered was which of the two possible halogenated *cis*-1,2-dihydrocatechols, *viz.* bromo-**1** or iodo-**1**, should be used as the starting material. In Chapter Two it was reported that alkyne **92** can be successfully coupled with iodobenzene, and given the order of reactivity of halide coupling partners in Sonogashira cross-couplings is alkenyl iodide > alkenyl bromide > aryl iodide,[1] it is possible that either bromo- or iodo-*cis*-1,2-dihydrocatechol could be used as a starting material. Generally, alkenyl bromides are considered to be more stable than the corresponding iodides, which can be light-sensitive, thermally unstable and susceptible to oxidation at the halogen. However, a consideration of previous syntheses of tricholomenyn A and harveynone, as discussed in Chapter One, suggests that the desired Sonogashira cross-coupling reaction will likely require the most activated of

coupling partners so as to ensure a successful result. Consequently, it was decided to commence the synthetic work described herein using the iodinated form of diol **1**.

3.1.2 The selectivity of epoxidation-nucleophilic ring-opening sequences applied to *cis*-1,2-dihydrocatechols

The regio- and stereo-chemical outcomes associated with the proposed epoxidation/ring-opening sequence involving the *cis*-diols could be anticipated with some confidence as a result of previous studies on substrates of this type.[2] Thus, of the two alkenyl double bonds within such dienes, only the di-substituted (non-halogenated) one undergoes epoxidation upon treatment with conventional electrophilic reagents such as *m*-CPBA and dimethyldioxirane (DDO). This is because the electron-withdrawing effect of the halogen ensures that the attached double bond is unreactive towards such reagents (Scheme 3.2). The diastereoselectivity of the epoxidation process is controlled by the steric effects exerted by both the protected hydroxyl group(s) attached to the cyclohexene ring and the epoxidising reagent used. Furthermore, the nucleophilic ring-cleavage of the epoxide so-formed could expected to take place exclusively at the allylic position for both electronic and steric reasons.[2]

Scheme 3.2**: The regiochemistry of epoxide formation and nucleophilic ring opening on cis-1,2-dihydrocatechols of general type **99

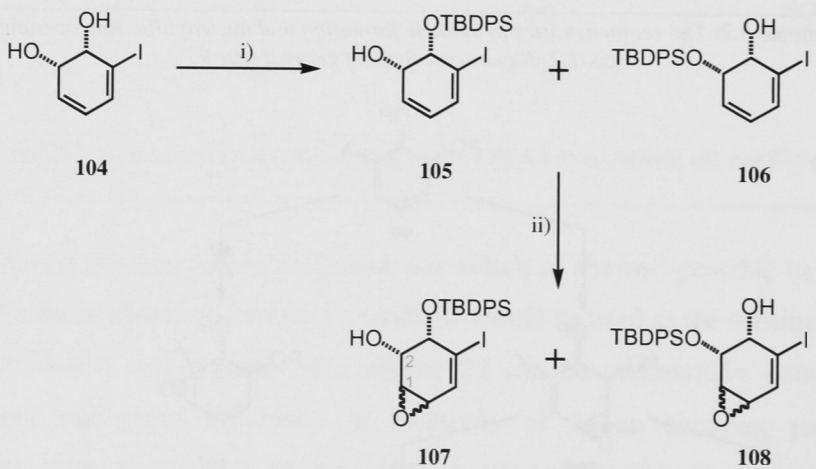


3.2 First Approach

3.2.1 Results and discussion

On the basis of the foregoing analysis, iodo-diol **104** was mono-protected using TBDPSCl in the presence of imidazole (Scheme 3.3). This afforded a 1:5 mixture of the expected mono-protected products **105** and **106** *via* a process that was judged to have proceeded cleanly by inspection of the ^{1}H NMR spectrum of the crude reaction mixture. Due to the unstable nature of these products, no attempts were made to separate them at this stage. Rather, the mixture was subjected to epoxidation using *m*-CPBA. Unfortunately, this led to the formation of a large number of products as judged by TLC and ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Nevertheless, two of the more significant products, compounds **107** and **108**, could be isolated, albeit in only 10% yield in each case. Attempts were made to improve the selectivity and efficiency of this reaction through the use of other epoxidising reagents such as mono-magnesium peroxyphthalate and DDO. Unfortunately, however, such efforts proved unsuccessful.

***Scheme 3.3**: Preparation of compounds **107** and **108** as part of the first approach to the synthesis of the cyclohexene core of (+)-tricholomenyn B*



Reagents and Conditions: i) TBDPSCl, imidazole, DCM, 18 °C, 1 h, quantitative yield, 1:5 ratio of **105**:**106**; ii) *m*-CPBA, DCM, 0 → 18 °C, 16 h, 10% **107**, 10% **108**.

Although the stereochemistries of the epoxides **107** and **108** were not determined, the data obtained on each compound were fully consistent with the assigned structures. Thus, the ^{1}H-^{1}H (COSY) NMR spectrum of compound **107** shows vicinal coupling

between the proton of the hydroxyl group and the adjacent ring-methine proton (H2), with a further vicinal coupling interaction being observed between the latter proton and the H1 epoxy proton. The low yields observed in this epoxidation reaction were considered most likely to result from oxidation of the iodine by *m*-CPBA. Nevetheless, given that there are examples in the literature of iodo-*cis*-dihydrocatechols undergoing efficient epoxidation,[3] it is possible that the protecting group strategy being used here was contributing to the problems being experienced. Accordingly, it was decided to examine alternate protecting group regimes in an effort to improve the outcomes of a reaction sequence starting from diol **104**.

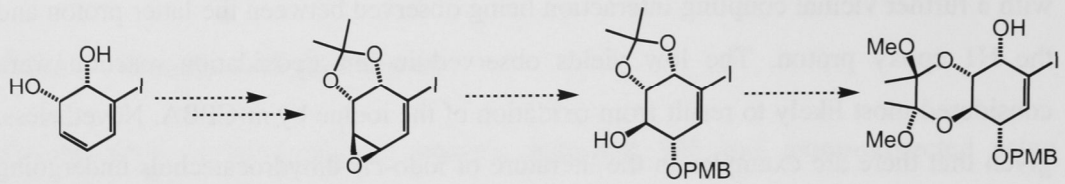
3.3 SECOND APPROACH

3.3.1 A different protecting group regime

The revised approach detailed here sought to utilise the known epoxide **109**[3] (which can be prepared in two steps and good yields from the corresponding diol **104**) and which would be subjected to ring opening using *p*-methoxybenzyl alcohol (PMB-OH) as the nucleophile (Scheme 3.4). This would then be followed by removal of the acetonide unit and re-protection of the liberated *trans*-diol as the butane-2,3-diacetal* and thus giving compound **111**. Such a regime was considered because the expected product, compound **111**, would incorporate a single free alcohol capable of being oxidised to the requisite ketone after the critical Sonogashira cross-coupling reaction had been carried out. Details of the efforts undertaken so as to try and implement such an approach are provided in the following section.

* The butane-2,3-diacetal protecting group is one of a suite of 1,2-diacetal protecting groups, primarily developed by the group of Ley, that can be used in the selective protection of *trans*-vicinal diols [4]. The preference for derivatisation of *trans*-diols (rather than *cis*-diols) arises from steric restraints and, to a greater degree, the anomeric effect exerted by the two acetal residues within this bifunctional protecting group [5].

***Scheme 3.4**: A second protecting group strategy*

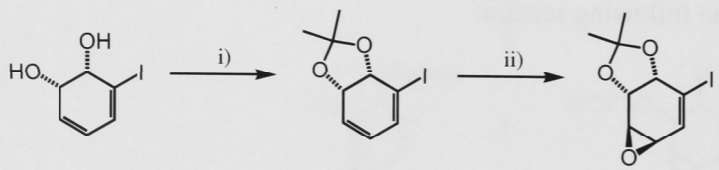


104 **109** **110** **111**

3.3.2 Results and discussion

The diol moiety associated with compound **104** was converted, under standard conditions and quantitative yield, into the corresponding acetonide **112**. Given the unstable nature of the latter compound, it was immediately subject to epoxidation to give the known compound **109**,[3] as a single diastereomer, in 77% yield (Scheme 3.5). The ^{1}H NMR spectrum of this material showed two three-proton singlets at δ 1.47 and 1.43 which were assigned to the protons of the two non-equivalent methyl groups associated with the acetonide moiety. Additionally, the signals seen at δ 3.61 (doublet of doublets, J = 3.7 and 2.1 Hz) and δ 3.19 (multiplet) are assigned to the protons attached to the epoxide ring. The assigned structure was also supported by the derived EI mass spectrum, which showed a molecular ion at m/z 294. An accurate mass measurement on this species established that it was of the expected composition, namely $C_9H_{11}IO_3$.

Scheme 3.5**: Preparation of iodo-epoxide **109



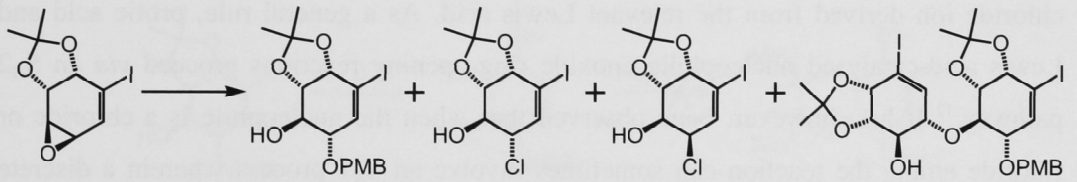
104 **112** **109**

Reagents and Conditions: i) 2,2-DMP, *p*-TsOH, 1.2 h, quantitative yield; ii) *m*-CPBA, $NaHCO_3$, DCM, 0 → 18 °C, 23 h,77%.

With epoxide **109** clearly in hand, the nucleophilic cleavage of the three-membered ring using PMB-OH was investigated (Scheme 3.6). As PMB-OH is not a strong enough nucleophile to effect spontaneous ring-opening of an epoxide, some form of activation is required and the most common approach is to add a protic or Lewis acid catalyst to

the reaction mixture. A variety of such catalysts were explored in an effort to achieve such an outcome and a summary of the results obtained is shown in Table 3.1. Both triflic acid[6] and $BF_3 \bullet Et_2O$[7] (Entries 1 and 2) proved to be too harsh, resulting in total decomposition of the substrate. In contrast, $[Rh(CO_2)_2Cl]_2$ (Entry 3), which is one of the few reported examples of a neutral species available for catalysing the ring-opening of epoxides,[8] proved to be ineffective in this case and led to the quantitative recovery of starting material **109**. When zinc(II) chloride[9] was used (Entry 4), the desired product **110**, was obtained albeit together with equal quantities of two other products, namely the dihalides **113** and **114**. The same trio of reaction products was also observed when indium trichloride[10] was used as the catalyst (Entry 5). Scandium(III) triflate proved to be the most suitable Lewis acid catalyst for the epoxide ring opening, giving a 6:1 mixture of desired product **110** and binary compound **115** (Entry 6).

Scheme 3.6**: All products observed from the ring-opening of epoxide **109



109 **110** **113** **114** **115**

***Table 3.1**: Catalysts explored in attempts to effect the nucleophilic ring-opening of epoxide **109** with PMB-OH*

		% yield				
Entry	Catalyst	**110**	**113**	**114**	**115**	Comments
1	Triflic acid	-	-	-	-	decomposition
2	$BF_3 \bullet Et_2O$	-	-	-	-	decomposition
3	$[Rh(CO_2)_2Cl]_2$	-	-	-	-	no reaction
4	$ZnCl_2$	26	34	30	-	poor selectivity
5	$InCl_3$	54	14	29	-	improved selectivity
6	**$Sc(OTf)_3$**	**60**	**-**	**-**	**24**	**best selectivity**

The structure of compound **110** was confirmed, *inter alia*, through IR spectroscopy which revealed a broad absorption band at 3464 cm^{-1} corresponding to the O-H

stretching of the hydroxy moiety. The two mutually coupled one-proton doublets (J = 11.3 Hz) appearing in the ^{1}H NMR spectrum of compound **110** at δ 4.66 and 4.54 are attributed to the two diastereotopic benzylic methylene protons.* The structures of di-halides **113** and **114** were assigned using both 1D and 2D NMR spectroscopic methods. A comparison of such data with those reported[11] for the analogous pair of dichlorides served to reinforce such assignments. The structure of the binary complex **115** is supported by the ^{1}H NMR spectrum of this material which displayed two one-proton multiplets at δ 6.58 and 6.50 corresponding to two alkenic protons. The low field signals associated with the PMB protecting group integrate to just four protons, thus indicating the presence of a single such residue. In addition, the ESI mass spectrum of this material shows a prominent ion at m/z 749, corresponding to the molecular ion plus sodium [*viz.* $(M + Na)^+$].

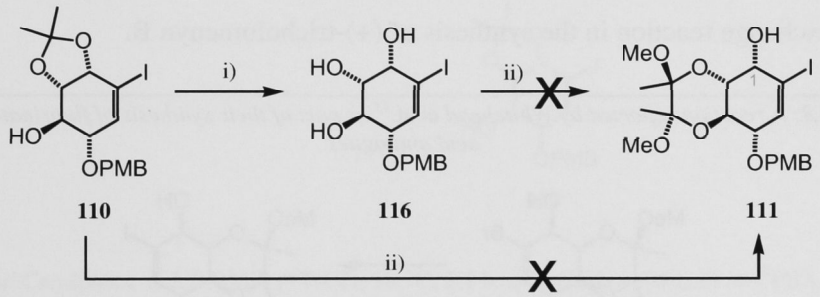
Both dihalides **113** and **114** arise as a result of nucleophilic attack on epoxide **109** by a chloride ion derived from the relevant Lewis acid. As a general rule, protic acid and Lewis acid-catalysed nucleophilic epoxide ring-opening reactions proceed *via* an S_N2 pathway.[12] It has, however, been observed that when the nucleophile is a chloride or fluoride anion, the reaction can sometimes involve an S_N1 process wherein a discrete allylic cation is involved as an intermediate.[2,11] Chloro-alcohol **114** is most likely formed as a result of such an S_N1 process, while the isomeric *trans*-chloro-alcohol **113** could be formed *via* either an S_N1 or S_N2 process. Binary compound **115** almost certainly arises as a result of the newly formed hydroxy group within product **110** acting as the nucleophile in the ring-opening reaction of a second molecule of the precursor epoxide **109**.

With alcohol **110** in hand, attention was turned to the removal of the acetonide residue and installation of the butane-diacetal protecting group, so as to leave the allylic alcohol at C1 as the only free alcohol residue present within the cyclohexenyl framework (Scheme 3.7). As acetal group installations and cleavages are both usually carried out in the presence of acid, efforts were initially directed towards the preparation of diacetal **111** directly from alcohol **110**. Unfortunately, when compound **110** was subjected to the conditions required to form diacetal **111**, *viz.* treatment with 2,3-butandione and

* In the starting material, *p*-methoxybenzyl alcohol, the benzylic methylene protons are equivalent and appear as a singlet at δ 4.59.

trimethylorthoformate in the presence of camphorsulfonic acid, the result was an extremely complex mixture containing a substantial number of products. So, with the aim of simply effecting acetonide cleavage to give triol **116**, compound **110** was exposed to Dowex H^+ resin. Whilst this reaction worked well on a small scale, on a larger one the reaction times required were greater than a month and impractical, therefore, from a synthetic perspective. Efforts to increase the reaction rate through increasing the temperature resulted in the concurrent removal of the PMB group. However, treatment of alcohol **110** with trichloroacetic acid in methanol at 18 °C for nine days delivered the desired triol **116** in 63% yield. When triol **116** was subjected to the previously mentioned diacetal forming conditions, an extremely complex mixture of products was again obtained. At this point, then, it was becoming apparent that a re-evaluation of the synthetic route being pursued was required.

Scheme 3.7**: Preparation of triol **116** and unsuccessful attempts to synthesise diacetal **111



Reagents and Conditions: i) TCA, MeOH, 18 °C, 9 d, 63%; ii) CSA, 2,3-butandione, MeOH, 80 °C, 2 – 6 h, complex mixture of products.

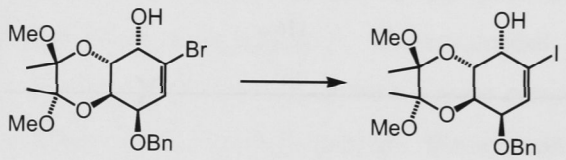
During the course of this research, an extremely relevant paper was published by Whitehead *et al.*[13] which prompted a reconsideration of which *cis*-1,2-dihydrocatechol, iodide or bromide, should be used in the synthesis of the cyclohexene core of (+)-tricholomenyn B. Whitehead's research and its implications for the work described in this thesis are discussed in the following section.

3.3.3 Whitehead's preparation of shikimic acid analogues

The 2004 paper published by Whitehead *et al.* is concerned with the synthesis of fluorinated shikimic acid analogues.[13] It describes some of the difficulties experienced in handling various alkenyl iodide precursors, a number of which bear a strong

structural resemblance to those described in this thesis. In a very neat way of accessing the synthetic advantages of both alkenyl iodides (more reactive, less stable) and bromides (more stable, less reactive), this group carried out the bulk of their synthetic work on the relevant and stable alkenyl bromides. Then, at the point where the alkenyl iodide functionality was required, a Finkelstein-type reaction was used to convert the bromide into the corresponding iodide (Scheme 3.8). Such methodology was first introduced by Buchwald,[14] and is not a Finkelstein reaction in the traditional sense as it does not proceed *via* an S_N2 process operating at an sp^3-hybridised carbon. However, like the Finkelstein reaction it is an equilibrium process, the position of which is determined by the differing solubilities of the relevant halide salts used in achieving the conversion.[14] This methodology offered the possibility of carrying out the synthesis of the cyclohexene target **67** using the bromo-*cis*-1,2-dihydrocatechol as the starting material, while still allowing access to the more reactive alkenyl iodide should it be required. Hence, the decision was made to investigate the feasibility of utilising this halogen exchange reaction in the synthesis of (+)-tricholomenyn B.

***Scheme 3.8**: A reaction reported by Whitehead* et al.[13] *as part of their synthesis of fluorinated shikimic acid analogues*



117 **118**

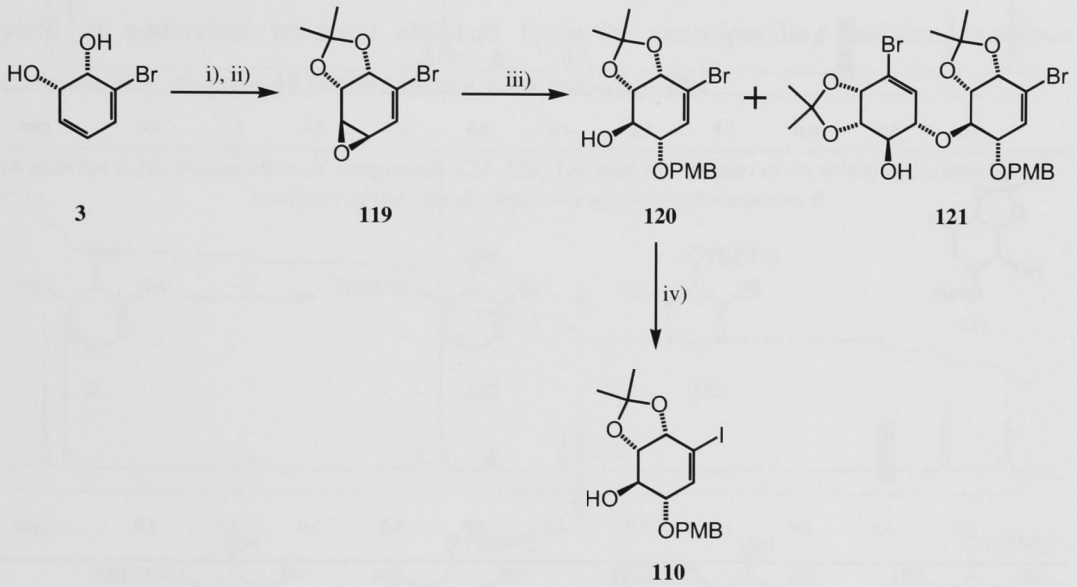
Reagents and Conditions: CuI, KI, *N,N'*-dimethylethylenediamine, *n*-BuOH, reflux, 72%.

3.3.4 Evaluating the potential of Buchwald's alkenic variation on the Finkelstein reaction

As an authentic sample of alkenyl iodide **110** had already been generated (see Section 3.3.2), it was decided to synthesise the corresponding alkenyl bromide **120** as a substrate for testing the Finkelstein-type reaction (Scheme 3.9). Accordingly, the known bomo-epoxide **119**[15] was prepared by established methods in two steps and quantitative yield from diol **3**. This can be contrasted with the 77% yield obtained when preparing the iodo-epoxide analogue of **119**, a situation that further reinforces the difference in stability between the two types of alkenyl halides relevant to the present work. Epoxide

119 was then subjected to $Sc(OTf)_3$-catalysed epoxide ring-opening to give alcohol **120** and binary compound **121** in unoptimised yields of 43% and 26%, respectively. The yields of the undesired binary compound **121** were higher in this case when compared to the analogous reaction involving the iodinated substrate. At this point, however, no attempts were made to suppress the formation of this byproduct.

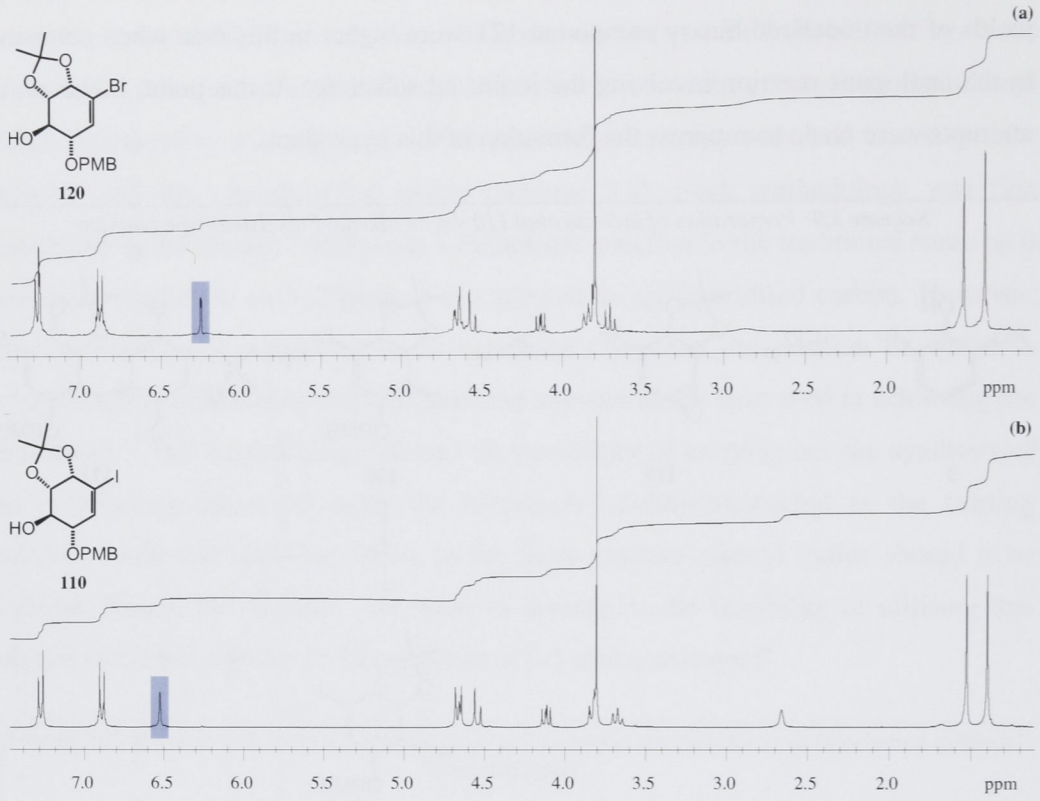
***Scheme 3.9**: Preparation of iodo-alcohol **110** via an alkenic Finkelstein-type reaction*



Reagents and Conditions: i) 2,2-DMP, *p*-TsOH, 18 °C, 1.2 h, quantitative yield; ii) *m*-CPBA, DCM, 0 → 18 °C, 18 h, quantitative yield; iii) PMB-OH, $Sc(OTf)_3$, 4 Å mol sieves, DCM, 0 °C, 3 h, 43% **120**, 26% **121**; iv) CuI, NaI, *N,N'*-dimethylethylenediamine, *n*-BuOH, 120 °C, 26 h, 83%.

The ^{1}H NMR spectrum of bromo-alcohol **120** (Figure 3.2a) featured a one-proton doublet at δ 6.23 corresponding to the alkenic proton. In contrast, in the ^{1}H NMR spectrum of the analogous iodo-alcohol **110** the resonance attributed to the alkenic proton appeared as a multiplet at δ 6.53 (Figure 3.2b). Clearly then, ^{1}H NMR spectroscopy could provide a simple and highly effective means for assessing the outcomes of attempts to effect the pivotal Finkelstein reaction. In the event, when bromo-alcohol **120** was subjected to the Finkelstein-type reaction conditions detailed above, then iodide **110** was obtained in 83% (at 100% conversion). Accordingly, this type of conversion seemed like one that could be exploited in the synthesis of the cyclohexene core of (+)-tricholomenyn B if required.

***Figure 3.2**: 300 MHz ^{1}H NMR spectra of bromoalcohol **120** (a) and iodoalcohol **110** (b) with the resonances arising from the alkenic protons highlighted in blue (spectra recorded in $CDCl_3$)*



3.4 First Protecting Group Strategy Revisited

3.4.1 Preamble

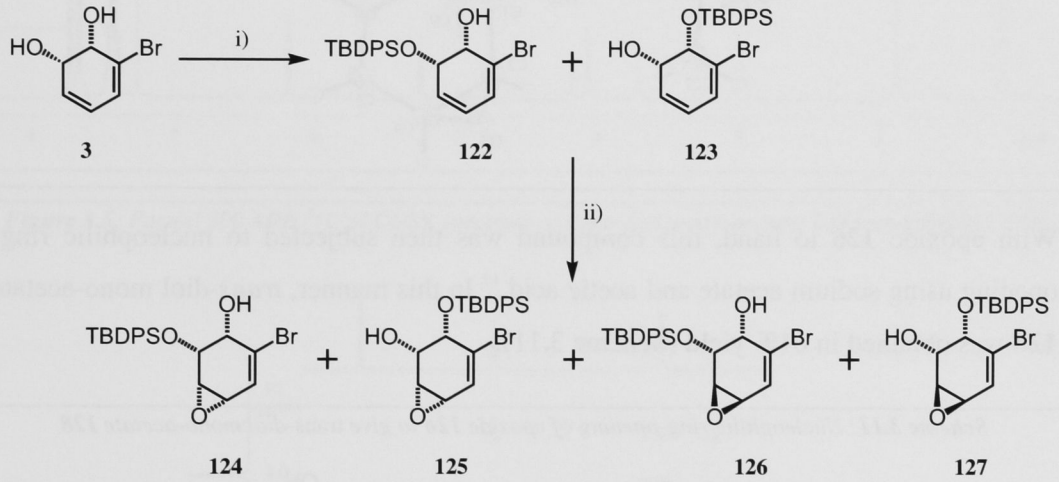
Given the potential for achieving an iodine-for-bromine exchange using Buchwald's protocols as described above, it was decided to begin the synthesis of the cyclohexene core of (+)-tricholomenyn B using the bromo-diol **3**. It was also decided to reinvestigate the original protecting group regime so as to establish if a change in starting material (*viz.* using bromo-diol **3** instead of congener **104**) meant this synthetic route was now feasible.

3.4.2 Results and discussion

On the basis of the foregoing, bromo-diol **3** was treated with a mixture of TBDPSCl and imidazole and by such means a 4:1 mixture of the regio-isomeric mono-ethers **122** and **123** was obtained in quantitative (combined) yield (Scheme 3.10). The selectivity

observed in this reaction was less than that associated with the analogous reaction of iodo-diol **104**, an outcome that can be attributed to the smaller atomic radius of bromine and the reduced capacity it thus has to exert a steric effect on the reaction. The unstable nature of products **122** and **123** meant that no attempts were made to separate them. Rather, the mixture was immediately subjected to epoxidation using *m*-CPBA and this afforded, in a combined yield of 99%, a 4:2:10:1 mixture of stereo- and regio-isomeric epoxides **124**, **125**, **126** and **127**. This contrasts dramatically with the 20% combined yield of equivalent products obtained from the corresponding reaction sequence (Scheme 3.3, on page 48) commencing with iodo-diol **104**.

***Scheme 3.10**: Preparation of compounds **124**, **125**, **126** and **127** as part of an initial approach to the synthesis of the cyclohexene core of (+)-tricholomenyn B*

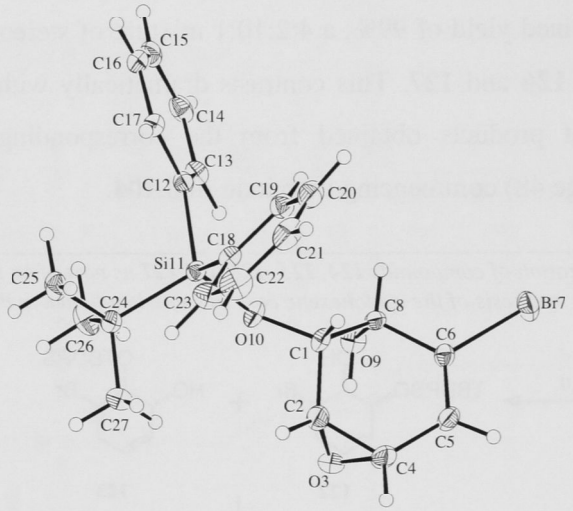


Reagents and Conditions: i) TBDPSCl, imidazole, DCM, quantitative (combined) yield, 4:1 ratio of **122**:**123**; ii) *m*-CPBA, DCM, 0 → 18 °C, 16 h, 99% (combined) yield, 4:2:10:1 ratio of **124**:**125**:**126**:**127**.

In order to assist the assignment of structures to the four epoxidation products **124** – **127**, precursors **122** and **123** were separated by column chromatography. While this resulted in substantial aromatisation of these materials, a moderately clean sample of compound **122** could be obtained and this was then subject to epoxidation to give a 2:5 mixture of epoxides **124** and **126**, respectively. This allowed the identification of the two products derived from the epoxidation of alkene **122** and, by deduction, those arising from the analogous reaction of congener **123**. The assignment of structures to each diastereomeric pair was established using a combination of 1D and 2D NMR techniques, in conjunction with a knowledge of the established stereochemical

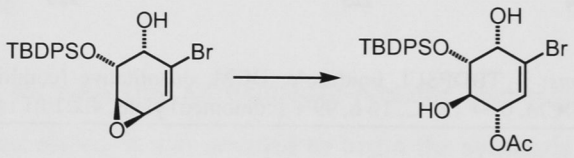
outcomes from epoxidation of cyclic alkenes using *m*-CPBA.* Additionally, the structure of compound **124** was confirmed by single-crystal X-ray crystallographic analysis (Figure 3.3). Further details of this analysis are provided in Appendix One.

Figure 3.3**: ORTEP derived from the single-crystal X-ray analysis of compound **124



With epoxide **126** to hand, this compound was then subjected to nucleophilic ring-opening using sodium acetate and acetic acid.[17] In this manner, *trans*-diol mono-acetate **128** was obtained in 61% yield (Scheme 3.11).

Scheme 3.11**: Nucleophilic ring-opening of epoxide **126** to give* trans*-diol mono-acetate **128



126 **128**

Reagents and Conditions: NaOAc, AcOH, 18 °C, 7 h, 61%.

The IR spectrum of this material showed a strong absorption band at 3454 cm^{-1} indicative of the O-H stretch of the hydroxy functional group and another at 1738 cm^{-1} corresponding to the C=O stretching of the ester carbonyl. The ^1H NMR spectrum (Figure 3.4) displayed a characteristic triplet at δ 5.26 that corresponds to the ring-methine proton associated with the carbon bearing the acetoxy unit. The ^1H-^1H

* The presence of an allylic hydroxyl moiety favours the formation of the *cis*-epoxide, while bulky allylic groups such as TBDPSO favour generation of the *trans*-product [16].

COSY spectrum (Figure 3.5) showed a strong correlation (blue highlight) between the alkenic proton and the aforementioned oxymethine proton and thus confirming the location of the acetate group.

Figure 3.4**: 300 MHz ^{1}H NMR spectrum of* trans-*diol mono-acetate* ***128 *(recorded in $CDCl_3$)*

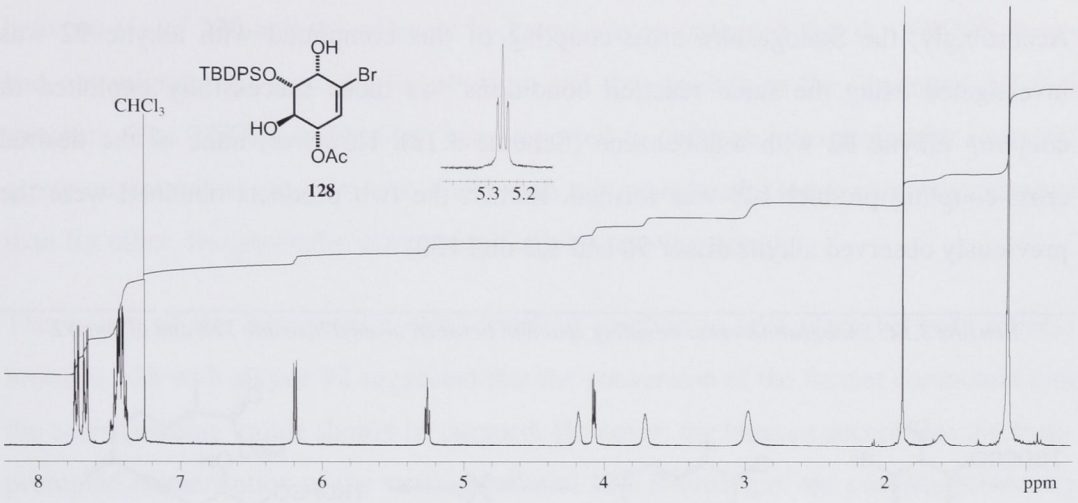
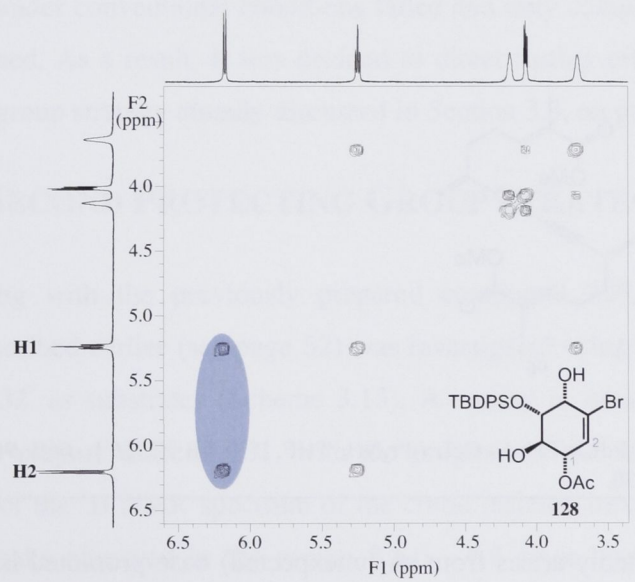


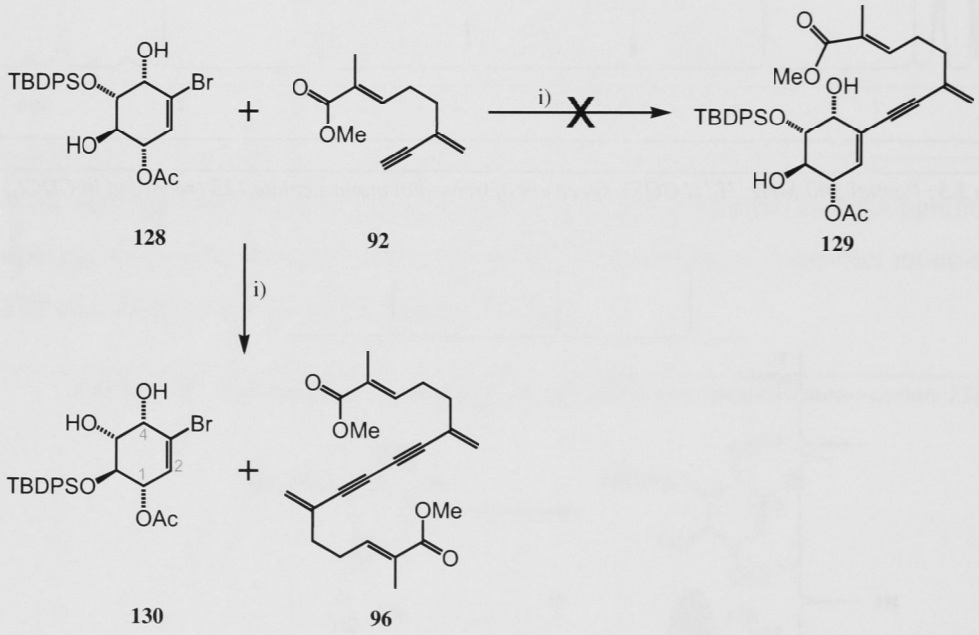
Figure 3.5**: Partial 300 MHz ^{1}H-^{1}H COSY spectrum of* trans-*diol mono-acetate* ***128 *(recorded in $CDCl_3$)*



Two possible methods were considered for the manipulation of diol **128** in order to carry it further along a reaction sequence leading to the target (+)-tricholomenyn B. Thus, the former compound might be converted, using the Finkelstein-type reaction, into the corresponding iodide, and as a prelude to trying the Sonogashira cross-coupling reaction with alkyne **92**. Alternatively, the cross-coupling could be attempted directly

using alkenyl bromide **128**. Previous studies, as described in Chapter Two, showed that iodobenzene can be successfully cross-coupled with alkyne **92** under Sonogashira conditions. Given that alkenyl bromides are generally considered more reactive coupling partners than aryl iodides,[1] it was anticipated that the reaction should proceed with compound **128** and not require its conversion to the corresponding alkenyl iodide. Accordingly, the Sonogashira cross-coupling of this compound with alkyne **92** was investigated using the same reaction conditions[18] as those successfully exploited in coupling alkyne **92** with iodobenzene (Scheme 3.12). However, none of the desired cross-coupling product **129** was formed. Rather, the two products obtained were the previously observed alkyne dimer **96** and 1,2-diol **130**.

Scheme 3.12**: Sonogashira cross-coupling reaction between alkenyl bromide **128** and alkyne **92



Reagents and Conditions: i) $PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, THF, 0 → 18 °C, 16 h, 66% **96**, quantitative yield of a 3:10 ratio of **128**:**130**.

Compound **130** undoubtedly arises from an (unexpected) base-promoted isomerisation of compound **128**, a process that resulted in a 3:10 mixture of isomers **128** and **130**. These compounds could not be separated *via* conventional flash chromatographic methods. However, a separation could be achieved under the conditions of GC-MS analysis. Both displayed molecular ions at *m/z* 503 and 505 in the 1:1 ratio expected for a mono-brominated species. This, together with the very similar chemical shifts

observed for both compounds in the ^{1}H NMR spectrum, indicated that product **130** was isomeric with the starting material **128**. The ^{1}H-^{1}H COSY spectrum of the mixture showed a correlation between the alkenyl proton (H2) of compound **130** and the ring-methine proton associated with the carbon bearing the acetate group and so indicating that the acetate group was still in the C1 position. In addition, a coupling of 5.1 Hz between H4 of **130** and the adjacent hydroxyl proton indicated that the TBDPS group had not migrated to the 4-allylic position, and thus leading to the illustrated 1,2-diol structure. The TBDPS residue has been reported to undergo *intra*-molecular hydroxyl group migrations in other systems,[19] although it is considered a less common occurrence than for other, less sterically encumbered, silyl protecting groups.

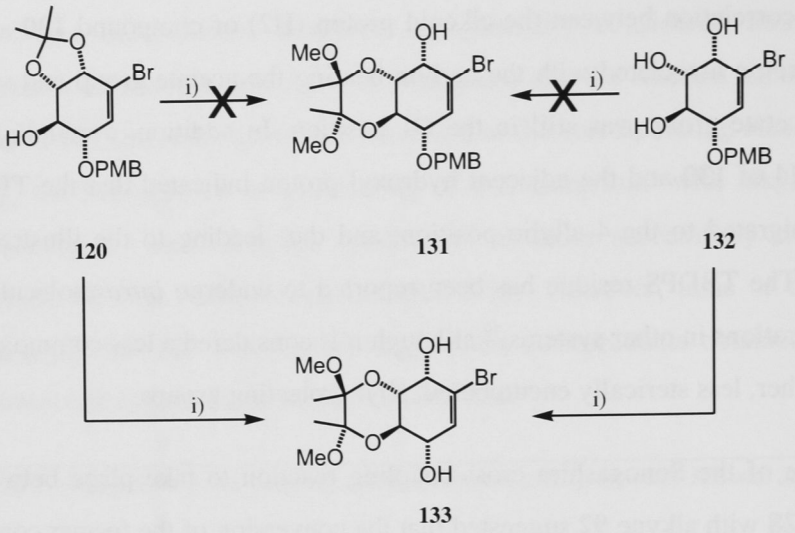
The failure of the Sonogashira cross-coupling reaction to take place between alkenyl bromide **128** with alkyne **92** suggested that the conversion of the former compound into the corresponding iodide should be pursued. However, the bigger concern was the base-promoted isomerisation of the starting material **128**. Blocking of the possible protecting group migration sites within alkenyl bromide **128** was attempted by converting this compound into the corresponding *bis*-MOM ether. However, all efforts to achieve such protection under conventional conditions failed and only complex mixtures of products were obtained. As a result, it was decided to direct further efforts towards the second protecting group strategy already discussed in Section 3.3, on page 49.

3.5 Second Protecting Group Strategy Revisited

Commencing with the previously prepared compound **120**, the *trans*-acetalisation process described earlier (see page 52) was investigated using both bromo-alcohol **120** and triol **132**[*] as substrates (Scheme 3.13). A variety of conditions were explored in attempts to prepare diacetal **131**, with the progress of the reaction being gauged by inspection of the ^{1}H NMR spectrum of the crude reaction mixture. Particular note was taken of peaks observed in the region δ 6.0 – 6.8 since signals in this region were presumed to correspond to the alkenic proton present in the relevant compounds.

[*] Triol **132** was prepared in 71% yield by treating acetonide **120** with TCA in THF/H_2O at 18 °C for 5 d.

Scheme 3.13**: Preparation of 1,4-diol **133** and unsuccessful attempts to prepare its diacetal derivative **131



Reagents and Conditions: 2,3-butandione, $HC(OMe)_3$, MeOH, CSA or TCA or AcOH or *p*-TsOH, 40 – 80 °C, 8 h – 72 h, 41 – 65% **133**.

The results arising from using differing reaction times, temperatures, reagent addition protocols and acid catalysts were the same regardless of whether substrate **120** or **132** was used. The outcomes of all relevant experiments can be summarised as follows:

♦ The application of standard literature conditions[4,20] to the substrate resulted in complete removal of the PMB protecting group, with the resultant formation of 1,4-diol **133** in yields of 41 – 65%.

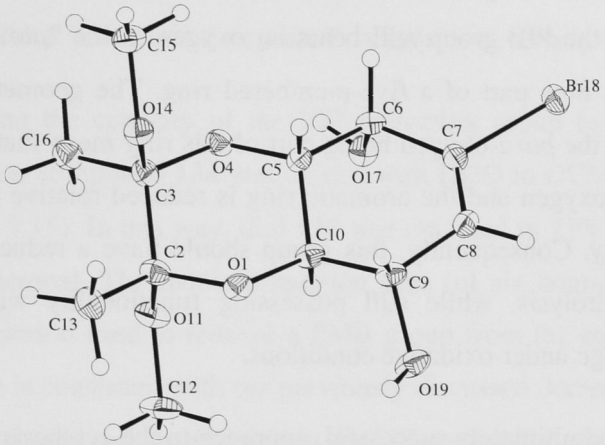
♦ Less forcing conditions resulted in a mixture of at least eight products, as judged by inspection of the number of alkenic resonances observed in the ^{1}H NMR spectrum of the crude reaction mixture.

The structure of 1,4-diol **133** was confirmed by a single-crystal X-ray crystallographic analysis (Figure 3.6). The cleavage of the PMB group provides for the possibility of the formation of regioisomeric *bis*-acetals, however only compound **133** was observed.

The outcomes described above indicated that the PMB protecting group was not compatible with the conditions required for installation of the *bis*-acetal protecting group. So, once again, a revised approach to the cyclohexene core of

(+)-tricholomenyn B was pursued. Details are presented in the following section of this chapter.

Figure 3.6**: ORTEP derived from the single-crystal X-ray analysis of compound **133

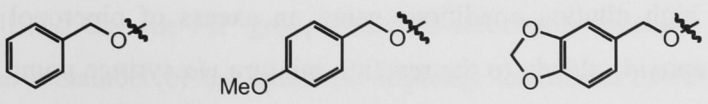


3.6 THIRD APPROACH TO THE SYNTHESIS OF THE CYCLOHEXENE CORE OF (+)-TRICHOLOMENYN B

3.6.1 Substituted benzyl ethers as hydroxy protecting groups

As a result of the observations described in the previous section, the use of the PMB moiety as an alcohol protecting group had to be abandoned. This was despite the advantage it might otherwise have offered of being able to be removed under mild oxidative conditions.[5,19] This contrasts with the situation with the parent benzyl protecting group (Figure 3.7) which can only be removed under more forcing conditions such as those employed in a dissolving metal reduction or a hydrogenolysis reaction. These differing properties arise as a consequence of the presence or absence of the electron-donating *p*-methoxy group. The disadvantage of the PMB group is that the *p*-methoxy residue reduces the stability of this group towards acid.

***Figure 3.7**: Different benzyl-derived hydroxy protecting groups*

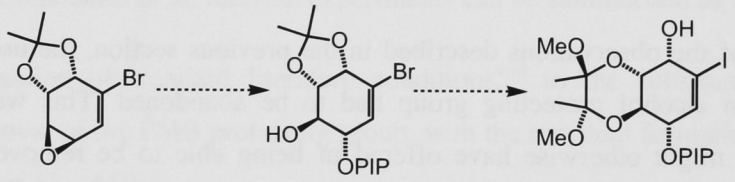


benzyl | *p*-methoxy benzyl | 3,4-methylenedioxy benzyl (piperonyl)

When considering alternatives to using the PMB moiety, it was decided to investigate the 3,4-methylenedioxy benzyl (PIP*) protecting group. The PIP group has not been used a great deal as an alcohol protecting group. Indeed, to the best of the author's knowledge, only one example of its use in this manner has been reported.[21] Like its PMB counterpart, the PIP group still bears an oxygen in the "*para*" position, but the relevant oxygen is now part of a five-membered ring. The geometric constraints that arise as a result of the *para*-oxygen being part of this ring mean that the orbital overlap between the *para*-oxygen and the aromatic ring is reduced relative to that encountered in the PMB moiety. Consequently, this group should have a reduced susceptibility to acid-catalysed hydrolysis, while still possessing functionality within it that would facilitate its cleavage under oxidative conditions.

So, in this final, and ultimately successful, approach to the synthesis of the cyclohexene core of (+)-tricholomenyn B, the route followed was analogous to that previously described, save for the substitution of the PMB group with the PIP moiety (Scheme 3.14).

***Scheme 3.14**: Plan for the third approach to the synthesis of the cyclohexene core of (+)-tricholomenyn B*



119 **134** **135**

3.6.2 Results and discussion

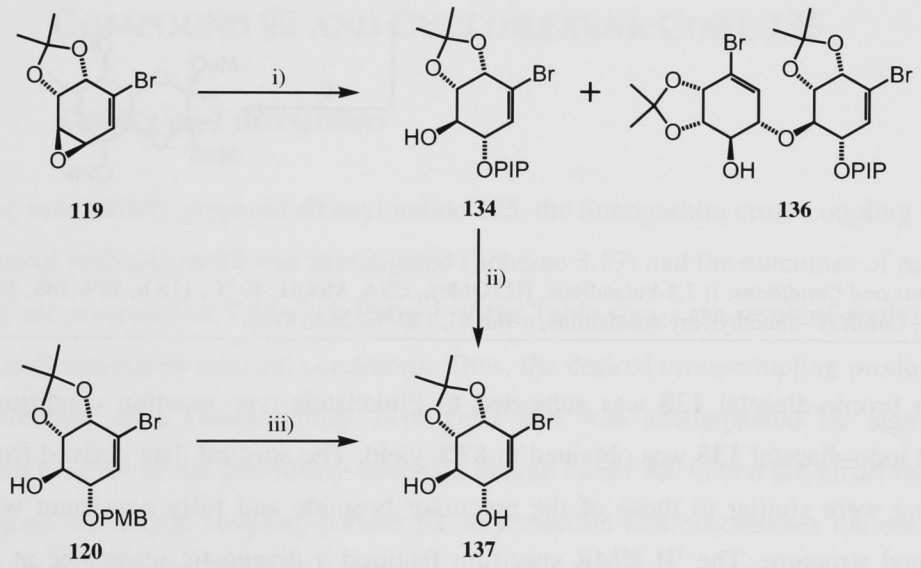
In seeking to implement the ideas noted above, the previously prepared bromo-epoxide **119** was subjected to $Sc(OTf)_3$-catalysed nucleophilic ring-opening by piperonol to give alcohol **134** and by-product **136** in 55% and 30% yields, respectively (Scheme 3.15). The formation of compound **136** could be partially suppressed by carrying out the reaction under high dilution conditions using an excess of piperonol and adding a solution of the epoxide slowly to the reaction mixture *via* syringe pump. The structure of the desired compound **134** was confirmed by, *inter alia*, the appearance of a

* The abbreviation is derived from the common name for 3,4-methoxybenzyl alcohol, which is piperonol.

prominent two-proton singlet at δ 5.95 in the ^{1}H NMR spectrum. This is assigned to the methylenedioxy protons of the newly introduced piperonyl group. The EI mass spectrum showed two molecular ions at *m/z* 400 and 398 in the 1:1 ratio expected for a mono-brominated species and an accurate mass measurement on that ion appearing at *m/z* 398 established that it was of the expected composition, namely $C_{17}H_{19}{}^{79}BrO_6$.

In order to examine the capacity of the PIP protecting group to be removed under oxidative conditions, compound **134** was treated with DDQ in DCM/water at 18 °C for six hours (Scheme 3.15). In this way, diol **137** was obtained in 77% yield together with the by-product piperonal. The required reaction time (of six hours) can be contrasted with the 2.5 hour period used to remove a PMB group from the equivalent compound **120**. This variation is consistent with the previously discussed decreased orbital overlap between the *para*-oxygen and the aryl ring in the PIP-containing system.

***Scheme 3.15**: Epoxide ring-opening of compound **119** with piperonol and formation of 1,2-diol **137** as a means of comparing PMB and PIP ether cleavage rates under oxidative conditions.*

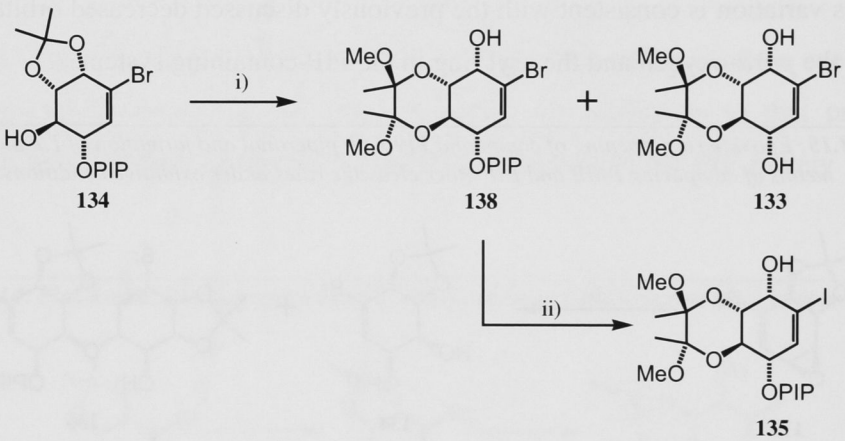


Reagents and Conditions: i) piperonol, $Sc(OTf)_3$, 4 Å mol. sieves, DCM, 0 °C, 3.25 h, 55% **134**, 30% **136**; ii) DDQ, DCM/H_2O, 18 °C, 6 h, 77%; iii) DDQ, DCM/H_2O, 18 °C, 2.5 h, 81%

Having established that the PIP group could be effectively removed under oxidative conditions, the remainder of the synthetic sequence leading to cyclohexene core **135** was carried out as shown in Scheme 3.16. Thus, alcohol **134** was subjected to *trans*-acetalisation to give diacetal **138** in 38% yield. This was accompanied by the previously observed diol **133** that was obtained in 33% yield. While the yield of the desired

product **138** is modest, this outcome still contrasts sharply with the previously noted inability of a PMB group to withstand the conditions required to effect *trans*-acetalisation. Numerous fruitless attempts were made to increase the yield associated with the conversion of compound **134** into diacetal **135**, but to no avail. Nevertheless, the spectral data obtained on acetal **138** were in full accord with the assigned structure. In particular, the ^{1}H NMR spectrum of this compound displayed two characteristic three-proton singlets at δ 3.31 and 3.27, while the ^{13}C NMR spectrum included two resonances at δ 48.1 and 48.0, all of which are attributed to the two methoxy groups of the butane-diacetal moiety.

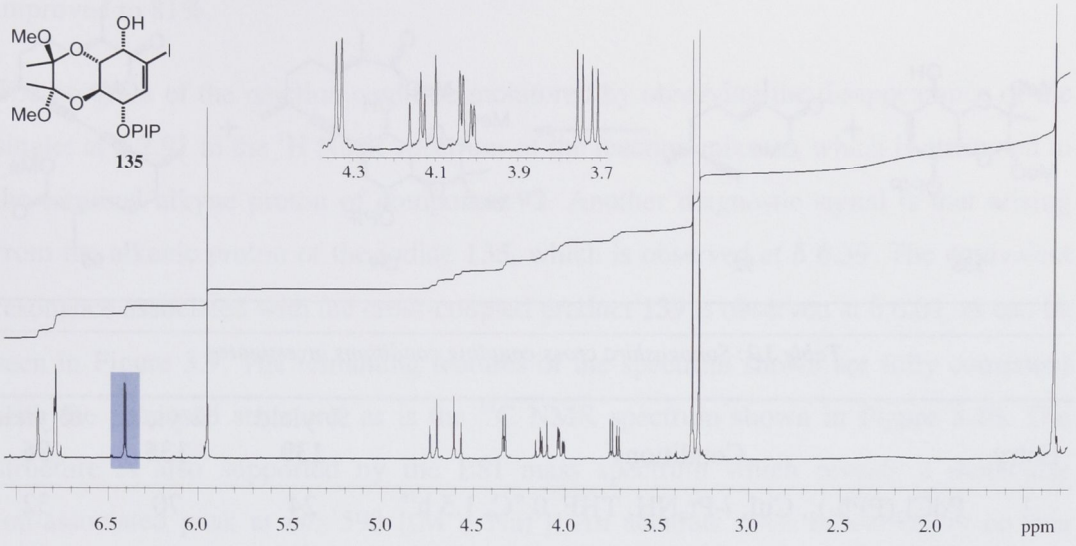
Scheme 3.16**: Preparation of alkenyl iodide **135



Reagents and Conditions: i) 2,3-butandione, $HC(OMe)_3$, CSA, MeOH, 40 °C, 118 h, 38% **138**, 33% **133**; ii) NaI, CuI, *N*,*N*'-dimethylethylenediamine, *n*-BuOH, 120 °C, 26 h, 87%.

When bromo-diacetal **138** was subjected to Finkelstein-type reaction conditions, the target iodo-diacetal **135** was obtained in 87% yield. The spectral data derived from this product were similar to those of the precursor bromide and fully consistent with the assigned structure. The ^{1}H NMR spectrum featured a diagnostic resonance at δ 6.39 (Figure 3.8, blue highlight) that was attributed to the alkenic proton, the chemical shift of which can be contrasted to that of the corresponding alkenic signal in the starting material **138** which appeared at δ 6.13.

***Figure 3.8**: 300 MHz ^{1}H NMR spectrum of iodo-diacetal **135** (recorded in $CDCl_3$)*

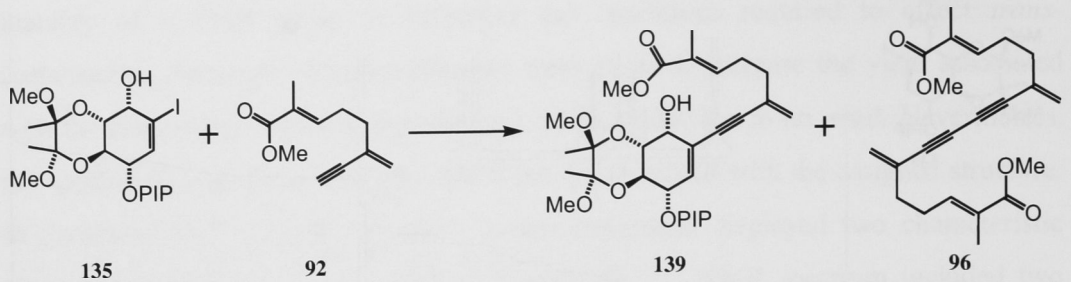


3.7 Refining the Sonogashira Cross-coupling Reaction Between *Ansa* Bridge-containing Compound 92 and Cyclohexene Core 135

3.7.1 Results and discussion

Having successfully prepared alkenyl iodide **135**, the Sonogashira cross-coupling of this compound with alkyne **92** was investigated (Scheme 3.17) and the outcomes of relevant studies are presented in Table 3.2. Entry 1 of the Table shows the result of applying the previously employed reaction conditions. Thus, the desired cross-coupling product **139** was obtained in a disappointing 24% yield and was accompanied by significant quantities (32%) of the previously observed alkyne dimer **96**. Given the effort required to prepare the alkyne coupling partner **92**, any reaction that necessitates the use of an excess of this compound is not desirable. Accordingly, efforts were made to avoid this side reaction. The alkyne dimerisation is mediated by the copper present in the reaction, and favoured by higher temperatures and dissolved oxygen in the reaction mixture. Entry 2 reveals that by careful choice of solvent and reaction temperature, and by exhaustively degassing the reaction mixture, the formation of dimer **96** can be almost completely suppressed.

Scheme 3.17**: Sonogashira cross-coupling between alkenyl iodide **135** and alkyne **92



135 **92** **139** **96**

***Table 3.2**: Sonogashira cross-coupling conditions investigated*

Entry	Conditions*	% yield **139**	% yield **135**	% yield **96**
1	$PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, THF, 0 °C, 1.5 h[18]	24	70	32
2	$PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, EtOAc, degassed, –10 °C, 2.5 h[23]	69	16	trace
3	$PdCl_2(PPh_3)_2$, piperidine, 70 °C, 1.75 h[24]	52	41	-
4	$Pd_2(dba)_3$, P(*t*-Bu)$_3$, Et_3N, 18 °C, 25 h[25]	20	27	-
5	$Pd(OAc)_2$, PPh_3, Et_3N, DMF/DMA, 18 °C, 6 h[26]	42	42	-
6	$PdCl_2$, Et_3N, acetone, ultrasound, <30 °C, 3 h[27]	32	14	22
7	$Pd(PPh_3)_4$, pyrrolidine, 18 °C, 48 h[28]	12	73	-
8	**$PdCl_2(PPh_3)_2$, $InCl_3$, piperidine, 60 °C, 4 h[22]**	**71**	**24**	**-**

Entries 3 – 8 illustrate the outcomes of pursuing another approach involving copper-free reaction conditions. As a general rule, copper-free Sonogashira cross-coupling procedures require more forcing conditions and longer reaction times than their copper-containing counterparts. Of the various conditions explored, the most successful proved to be that defined in Entry 8 of the Table, where the Lewis acid indium trichloride† is used to promote the desired cross-coupling reaction. In this way, the desired product **139** was obtained in 71% yield. These reaction conditions have proven to be extremely

* All reactions were carried out on the same scale using one equivalent of compound **135** and 1.5 equivalents of alkyne **92**. No unreacted **92** was recovered in any case.

† These reaction conditions were based on work published by Sakai *et al.*, which describes the novel use of indium tribromide as a co-catalyst in a copper-free Sonogashira cross-coupling reaction [22]. While the role of the $InBr_3$ has yet to be established, the authors suggest that it facilitates the reaction by initially coordinating to the alkyne π bond. Thus, the acidity of the terminal proton is increased, leading to proton abstraction by the amine base present in the reaction mixture. The resulting alkynyl-indium species could then participate in the cross-coupling reaction in much the same fashion as a copper acetylide species would under more conventional reaction conditions.

reliable and the yields obtained when the reaction was carried out on larger scales improved to 81%.

The progress of the reaction could be monitored by observing the disappearance of the singlet at δ 2.91 in the ^{1}H NMR spectrum of the reaction mixture, which is attributed to the terminal alkyne proton of compound **92**. Another diagnostic signal is that arising from the alkenic proton of the iodide **135**, which is observed at δ 6.39. The equivalent resonance associated with the cross-coupled product **139** is observed at δ 6.07, as can be seen in Figure 3.9. The remaining features of the spectrum shown are fully consistent with the proposed structure, as is the ^{13}C NMR spectrum shown in Figure 3.10. The structure is also supported by the ESI mass spectrum which reveals a molecular ion-associated peak at *m/z* 593 [(M + Na)$^{+}$]. An accurate mass measurement on this species established that it was of the expected composition, namely $C_{31}H_{38}NaO_{10}$. The acquisition of compound **139** represents a very significant milestone, as it incorporates the complete carbon skeleton of (+)-tricholomenyn B.

***Figure 3.9**: 300 MHz ^{1}H NMR spectrum of cross-coupled product **139** (recorded in $CDCl_3$)*

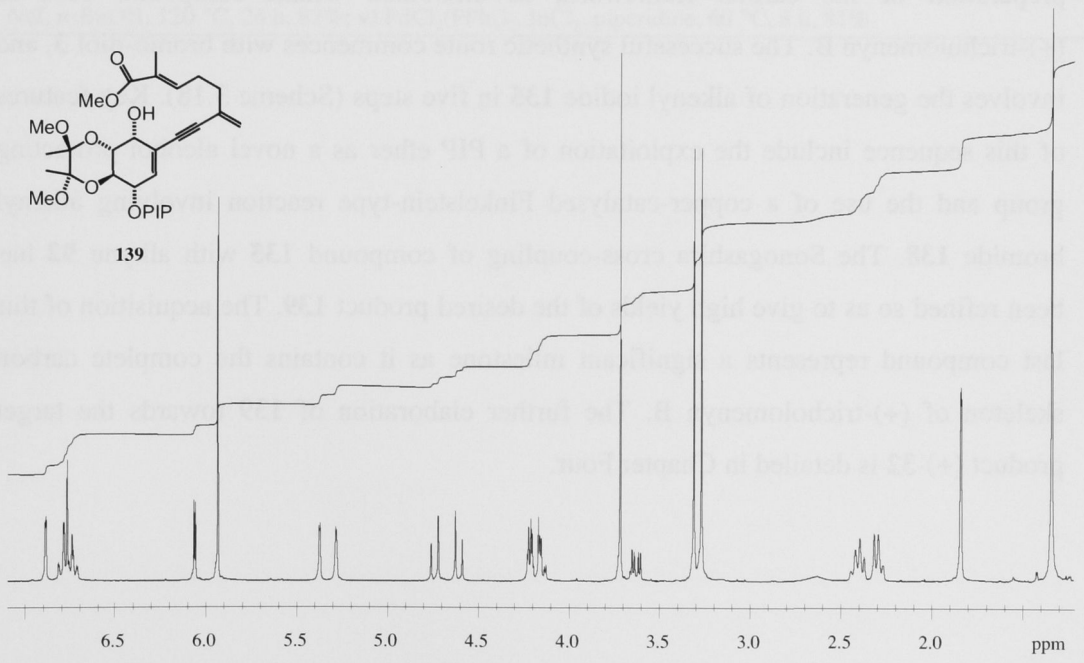
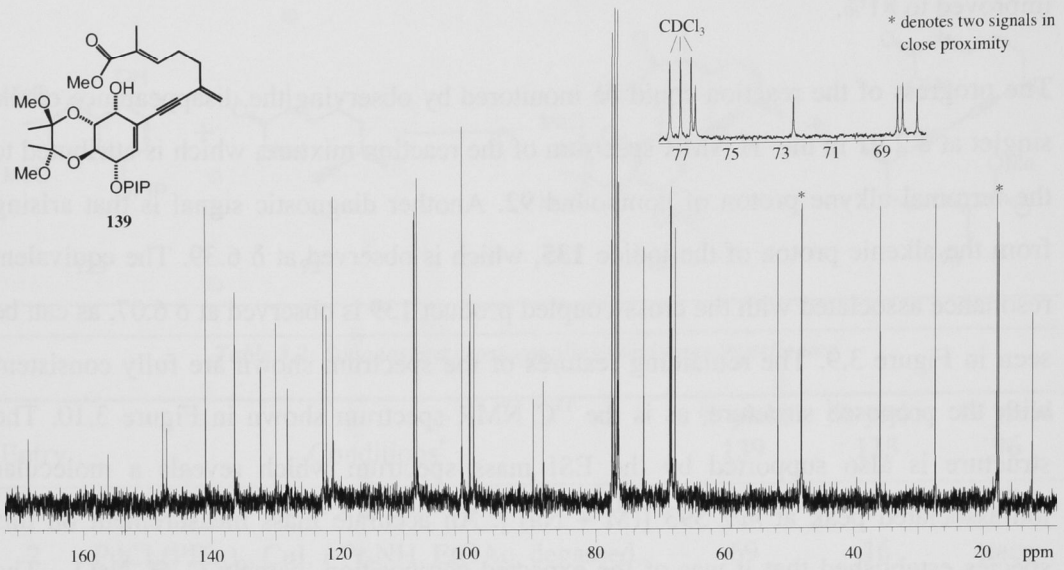


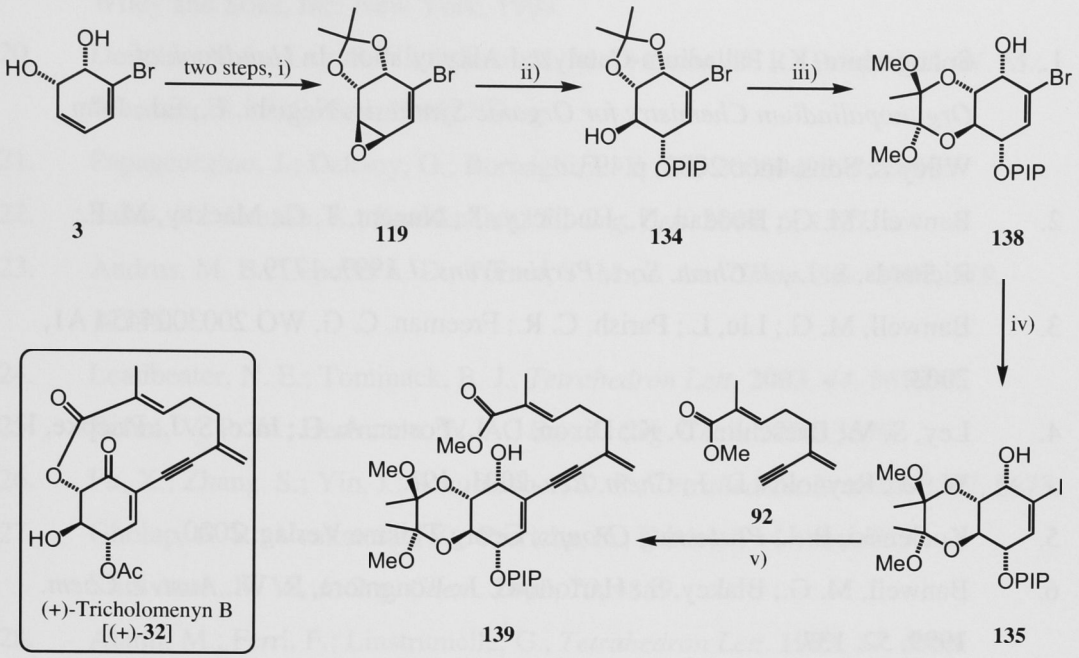
***Figure 3.10**: 75 MHz ^{13}C NMR spectrum of cross-coupled product **139** (recorded in $CDCl_3$)*



3.8 CONCLUSIONS

Three different approaches have been explored in the efforts directed towards the preparation of the carbon framework, as embodied within compound **139**, of (+)-tricholomenyn B. The successful synthetic route commences with bromo-diol **3**, and involves the generation of alkenyl iodide **135** in five steps (Scheme 3.18). Key features of this sequence include the exploitation of a PIP ether as a novel alcohol protecting group and the use of a copper-catalysed Finkelstein-type reaction involving alkenyl bromide **138**. The Sonogashira cross-coupling of compound **135** with alkyne **92** has been refined so as to give high yields of the desired product **139**. The acquisition of this last compound represents a significant milestone as it contains the complete carbon skeleton of (+)-tricholomenyn B. The further elaboration of **139** towards the target product (+)-**32** is detailed in Chapter Four.

Scheme 3.18**: Successful synthetic sequence leading to compound **139



Reagents and Conditions: i) a) 2,2-DMP, *p*-TsOH, 18 °C, 1.2 h, quantitative yield; b) *m*-CPBA, DCM, 0 → 18 °C, 18 h, quantitative yield; ii) PIP-OH, $Sc(OTf)_3$, 4 Å mol. sieves, DCM, 0 °C, 3.25 h, 55%; iii) 2,3-butandione, $HC(OMe)_3$, CSA, MeOH, 40 °C, 118 h, 38%; iv) CuI, *N,N'*-dimethylethylenediamine, NaI, *n*-BuOH, 120 °C, 26 h, 87%; v) $PdCl_2(PPh_3)_2$, $InCl_3$, piperidine, 60 °C, 8 h, 81%.

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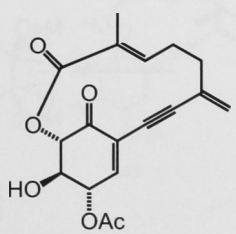
STUDIES DIRECTED TOWARDS COMPLETION OF THE SYNTHESIS OF (+)-TRICHOLOMENYN B

*This chapter details work directed towards the elaboration of compound **139** to the final target (+)-**32**. Difficulties encountered with various protecting group manipulations are described, as are (unsuccessful) attempts to carry out the pivotal macrolactonisation step. Several possible solutions to such problems are described.*

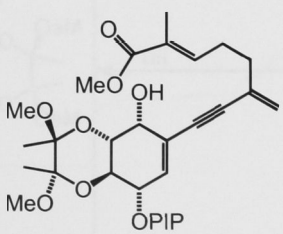
4.1 PREAMBLE

With the pivotal intermediate **139** (Figure 4.1) available *via* the protocols detailed in the previous chapters, attention could be turned towards efforts to complete a synthesis of (+)-tricholomenyn B [(+)-**32**]. This required the oxidation of the unprotected allylic alcohol within compound **139** to the corresponding ketone, as well as relevant protecting group manipulations to allow for formation of the macrolactone functionality and installation of the acetate group. Efforts to carry out such manipulations are described in the following sections of this, penultimate, Chapter.

Figure 4.1**: Final target (+)-tricholomenyn B [(+)-**32**] and the late-stage intermediate compound **139



(+)-**32**

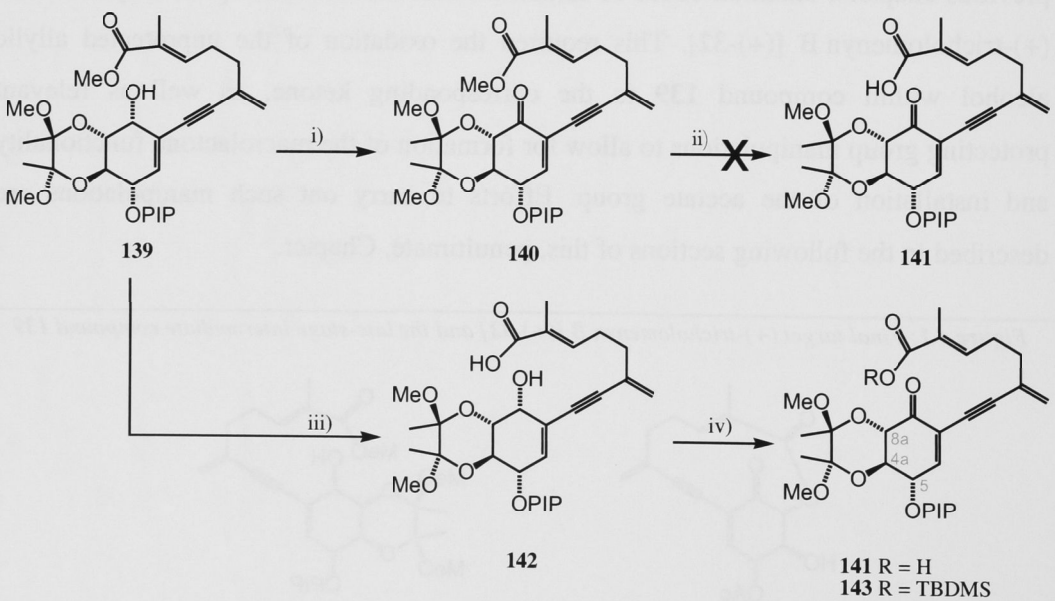


139

4.2 Results and Discussion

Alcohol **139** was oxidised with Dess-Martin periodinane to give ketone **140** in 55% yield (Scheme 4.1). The ^{13}C NMR spectrum of the latter compound featured a signal at δ 189.4 which was attributed to the newly formed ketone carbon. The assigned structure was also supported by the ESI mass spectrum, which revealed a molecular ion-associated peak at *m/z* 591 $[(M + Na)^+]$. An accurate mass measurement on this species established that it possessed the expected molecular formula, namely $C_{31}H_{36}NaO_{10}$. A variety of conditions were then explored in an effort to convert this methyl ester into the corresponding carboxylic acid **141**. However, these all led either to the quantitative recovery of starting material (when lithium ethanethiolate[1] or lithium iodide[2] was used) or decomposition of the substrate (when either sodium hydroxide,[3] lithium hydroxide[4] or sodium cyanide[5] was used). On the other hand, when allylic alcohol **139** was treated with lithium hydroxide, the reaction proceeded smoothly to give carboxylic acid **142** in 71% yield. The ^{13}C NMR spectrum of the latter compound showed, *inter alia*, only two signals [at δ 48.1(1) and 48.0(5)] corresponding to methoxy methyl carbons.

Scheme 4.1**: Synthetic efforts directed towards the allylic oxidation and saponification of compound **139



139 **140** **141**

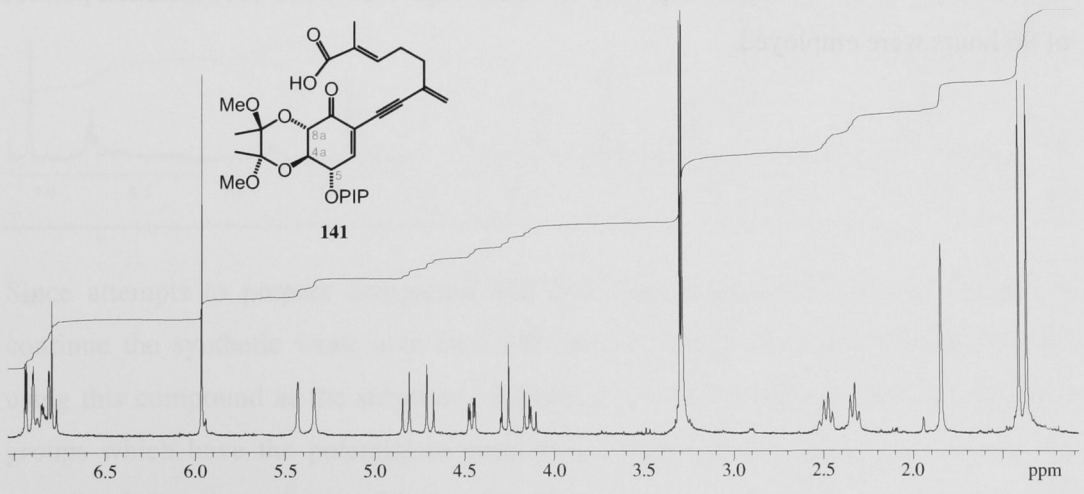
142

141 R = H
143 R = TBDMS

Reagents and Conditions: i) Dess-Martin periodinane, DCM, 0 → 18 °C, 18 h, 55%; ii) $LiSC_2H_5$, DMPU, 55 °C, 22 h (only starting material recovered); LiI, pyridine, reflux, 24 h (only starting material recovered); NaOH, $EtOH/H_2O$, 18 °C, 1 h (decomposition); $LiOH{\bullet}H_2O$, H_2O/THF/MeOH, 18 °C, 0.6 h (decomposition); NaCN, DMPU, 115 °C, 1 h (decomposition); iii) $LiOH{\bullet}H_2O$, H_2O/THF/MeOH, 18 °C, 18 h, 71%; iv) TBDMSCl, imidazole, THF, 18 °C, 1.5 h, then Dess-Martin periodinane, pyridine, DCM, 0 → 18 °C, 16 h, 46% **141**, 27% **143**.

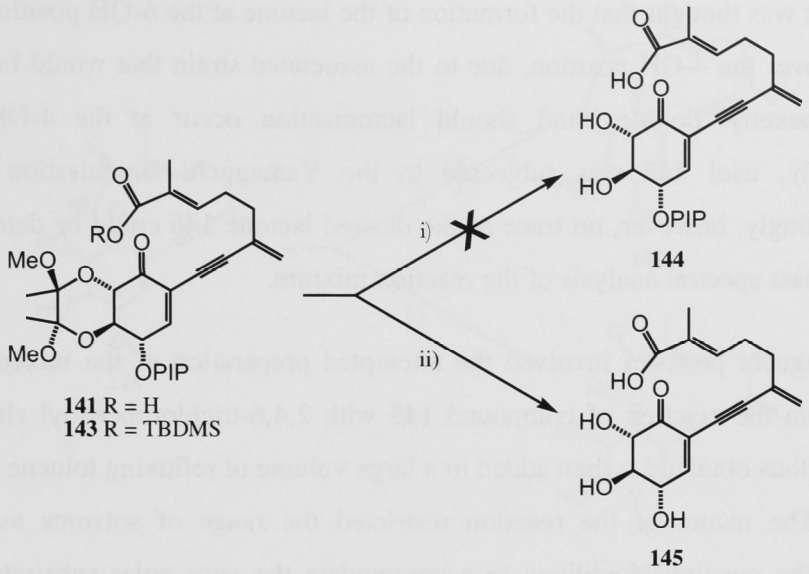
Having established that saponification of the methyl ester needed to be carried out on allylic alcohol **139** and not enone **140**, the carboxylic acid, **142**, derived from the former ester was then successfully oxidised to the corresponding ketone **141** using Dess-Martin periodinane. As difficulties were experienced in separating compound **141** from the residues associated with this oxidant, other reagents such as TPAP,[6] MnO_2[7] and $BaMnO_4$[8] were also investigated. However, none of these reagents was able to oxidise the allylic alcohol, a situation that may reflect the rather sterically congested environment around the hydroxy moiety. In an effort to circumvent the above-mentioned purification difficulties, compound **142** was first treated with TBDMSCl to form the corresponding TBDMS-ester which was then oxidised with Dess-Martin periodinane. With the carboxylic acid functionality masked as the TBDMS-ester, an aqueous base extraction step was able to be included in the work-up of the oxidation reaction, thereby removing the acidic residues associated with the oxidising reagent. The crude samples of compound **143** thus obtained were subjected to flash column chromatography and, as was expected, the acidic nature of the silica gel effected a partial removal of the TBDMS group. Thus, both compounds **141** and **143** were isolated as a result of such manipulations. As both products could be used directly in the next step of the synthesis, no attempts were made to alter the work-up and purification procedures to obtain a single product from this reaction. The ^1H NMR spectrum of ketone **141** (Figure 4.2) features three one-proton signals at δ 4.46 (H5), 4.27 (H8a) and 4.13 (H4a), which are assigned to the three ring methine protons and display coupling constants consistent with a *trans-trans* relationship ($J_{H5\text{-}H4a}$ = 8.4 and $J_{H4a\text{-}H8a}$ = 11.4 Hz).

***Figure 4.2**: 300 MHz ^1H NMR spectrum of ketone **141** (recorded in $CDCl_3$)*



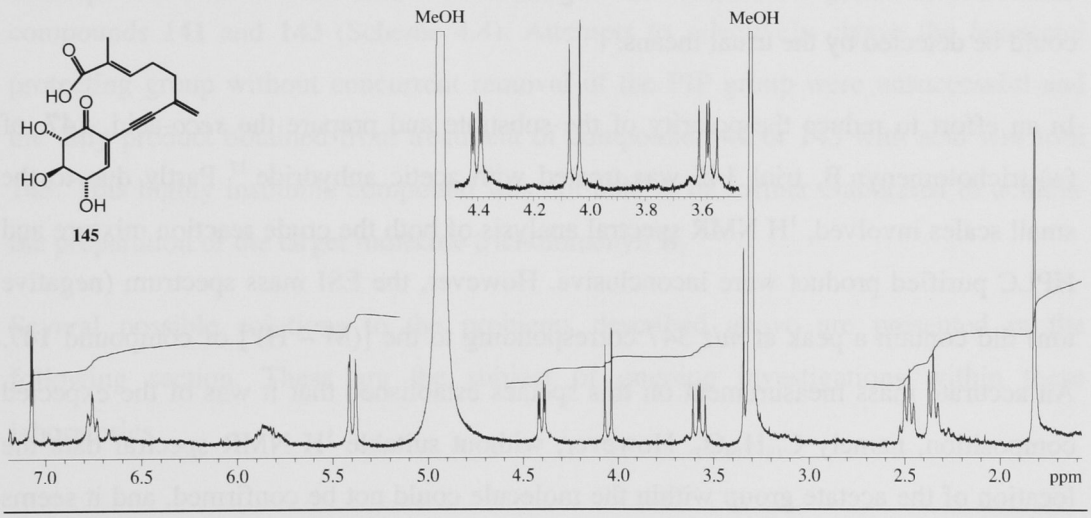
The next step investigated was the cleavage of the butane-diacetal group present in compounds **141** and **143** and concurrent removal of the TBDMS ester in compound **143** to give diol **144**. Cleavage of the butane-diacetal group is frequently accomplished using aqueous trifluoroacetic acid.[9] Unfortunately, however, treatment of compound **141** or **143** with trifluoroacetic acid not only resulted in the required transformation(s) occurring but also removal of the PIP group and so producing triol **145** (Scheme 4.2). Titanium tetrachloride has been reported to be an effective Lewis acid for promoting the cleavage of the *bis*-acetal group.[10] In the present case, however, use of this reagent led to decomposition of the substrate, as did treatment with tin(II) chloride.[11] By using ^{1}H NMR spectroscopy to monitor the reaction, it was determined that when either compound **141** or **143** was treated with acids such as camphorsulfonic acid[12] and pyridinium *p*-toluenesulfonate,[13] the PIP group was removed at a faster rate than the butane-diacetal group. The ^{1}H NMR spectrum of triol **145** (Figure 4.3) featured two single-proton resonances at δ 7.07 and 6.76 which are attributed to the two β-protons present in the α,β-unsaturated carbonyl systems. The IR spectrum of this compound was dominated by a strong absorption band at 3375 cm^{-1} that is attributed to O-H bond of the three hydroxy groups as well as the carboxylic acid moiety. The assigned structure was also supported by the ESI mass spectrum (recorded in negative ion mode), which showed a molecular ion-associated peak at *m/z* 305 $[(M - H)^{-}]$. An accurate mass measurement on this species established that it was of the expected composition, namely $C_{16}H_{17}O_6$. Triol **145** proved to be a difficult compound to handle, being highly insoluble in many organic solvents and only sparingly soluble in MeOH. Indeed, a sufficiently concentrated sample of compound **145** could not be prepared so as to obtain satisfactory ^{13}C NMR data. This proved to be the case even when accumulation periods of 96 hours were employed.

Scheme 4.2**:Synthetic sequence leading to the preparation of triol **145



Reagents and Conditions: i) TFA, DCM/H_2O, 18 °C, 2 h (**145** only product isolated); $TiCl_4$, DCM, –10 °C, 0.2h (decomposition); $SnCl_2 \bullet H_2O$, DCM/H_2O, 18 °C, 16 h (decomposition); PPTS, MeOH, 18 °C, 72 h (**145** only product isolated); CSA, MeOH, 60 °C, 48 h (**145** only product isolated); CSA, ethyleneglycol, MeOH, 40 °C, 48 h (**145** only product isolated); ii) TFA, DCM/H_2O, 18 °C, 2 h, 67% from **141**, 68% from **143**.

***Figure 4.3**: 300 MHz ^{1}H NMR spectrum of triol **145** (recorded in CD_3OD)*



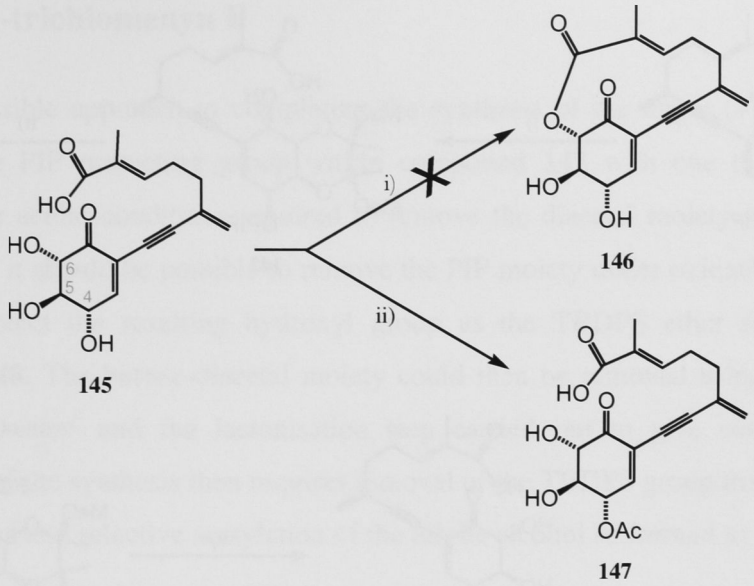
Since attempts to prepare compound **144** had been unsuccessful, it was decided to continue the synthetic work with triol **145** and investigate the key lactonisation step using this compound as the substrate (Scheme 4.3). Compound **145** has three hydroxy groups which have the potential to participate in the lactonisation step, however the associated ring strain that would arise from lactonisation onto 5-OH (see structure **145**,

Scheme 4.3) meant that the possibility of this occurring was considered extremely unlikely. It was thought that the formation of the lactone at the 6-OH position would be favoured over the 4-OH position, due to the associated strain that would be placed on the cyclohexenyl double bond should lactonisation occur at the 4-OH position. Accordingly, triol **145** was subjected to the Yamaguchi lactonisation protocol.[14] Disappointingly, however, no trace of the desired lactone **146** could be detected by ^{1}H NMR or mass spectral analysis of the reaction mixture.

The Yamaguchi protocol involved the attempted preparation of the mixed anhydride arising from the reaction of compound **145** with 2,4,6-trichlorobenzoyl chloride. The anhydride thus obtained is then added to a large volume of refluxing toluene (containing DMAP). The nature of the reaction restricted the range of solvents available for changing the reaction conditions to accommodate the very polar substrate involved. Modifications such as dissolving the mixed anhydride in THF or acetonitrile before adding it to the DMAP/toluene solution had no effect on the outcome of the reaction. Attempts were also made to prepare lactone **146** using a minor modification of a lactonisation procedure developed by Yamamoto *et al.*[15] and in which a solution of triol **145** in THF was slowly added to a large volume of a $Sc(OTf)_3$ and acetic anhydride[16] solution in refluxing acetonitrile. Once again, however, no trace of the desired product could be detected by the usual means.

In an effort to reduce the polarity of the substrate and prepare the *seco*-acid, **147**, of (+)-tricholomenyn B, triol **145** was treated with acetic anhydride.[17] Partly due to the small scales involved, ^{1}H NMR spectral analysis of both the crude reaction mixture and HPLC purified product were inconclusive. However, the ESI mass spectrum (negative ion) did contain a peak at *m/z* 347 corresponding to the $[(M - H)^-]$ of compound **147**. An accurate mass measurement on this species established that it was of the expected composition, namely $C_{18}H_{19}O_7$. However, without suitable ^{1}H NMR spectral data the location of the acetate group within the molecule could not be confirmed, and it seems likely that the reaction would have resulted in the formation of a mixture of products with acetylation also occurring at other than the desired position on the cyclohexene ring.

Scheme 4.3**: Attempted synthetic manipulations of triol **145



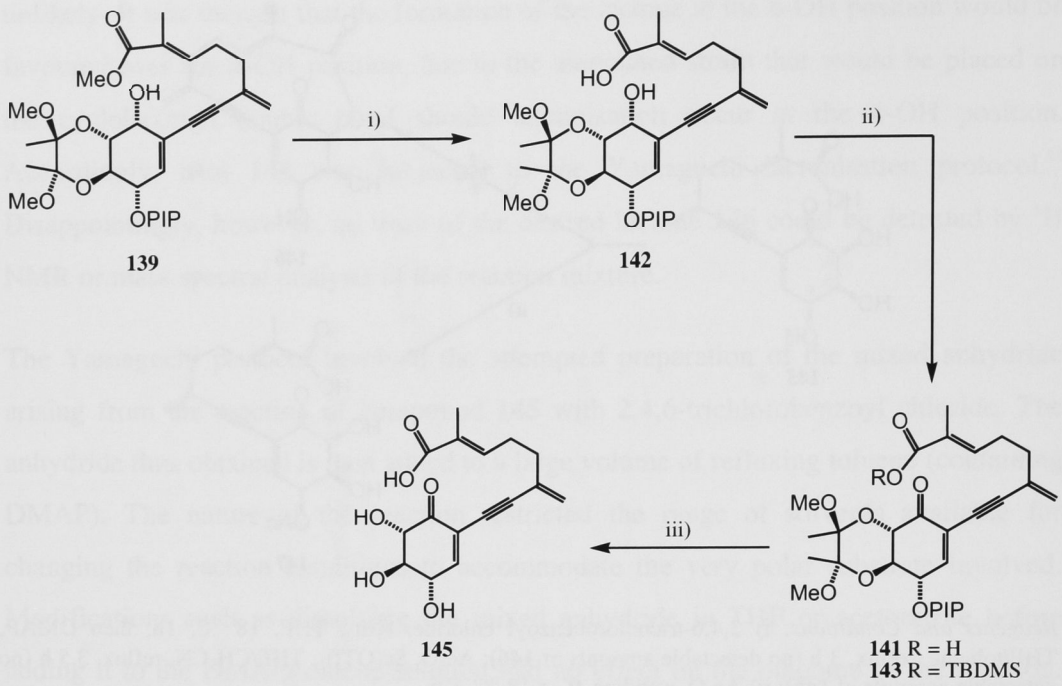
Reagents and Conditions: i) 2,4,6-tricholorobenzoyl chloride, NEt_3, THF, 18 °C, 1h, then DMAP, THF/toluene, reflux, 3 h (no detectable amounts of **146**); Ac_2O, $Sc(OTf)_3$, THF/CH_3CN, reflux, 3.5 h (no detectable amounts of **146**); ii) Ac_2O, pyridine, 0 → 18 °C, 8 h.

4.3 CONCLUSIONS

Beginning with compound **139** the necessary synthetic steps were carried out to prepare compounds **141** and **143** (Scheme 4.4). Attempts to selectively cleave the *bis*-acetal protecting group without concurrent removal of the PIP group were unsuccessful and the only product obtained from treatment of compound **141** or **143** with acid was triol **145**. This highly insoluble compound was not able to be further elaborated to achieve the preparation of the target molecule tricholomenyn B.

Several possible solutions to the problems described above are presented in the following section. These are the subject of ongoing investigations within these laboratories.

Scheme 4.4**: Preparation of triol **145** from Sonogashira cross-coupling product **139



139 **142** **145**

141 R = H
143 R = TBDMS

Reagents and Conditions: i) LiOH•H_2O, H_2O/THF/MeOH, 18 h, 71%; ii) TBDMSCl, imidazole, THF, 18 °C, 1.5 h, then Dess-Martin periodinane, pyridine, DCM, 0 → 18 °C, 46% **141**, 27% **143**; iii) TFA, DCM/H_2O, 18 °C, 2 h, 67% from **141**, 68% from **143**.

4.4 Future Work: Completion of the Synthesis

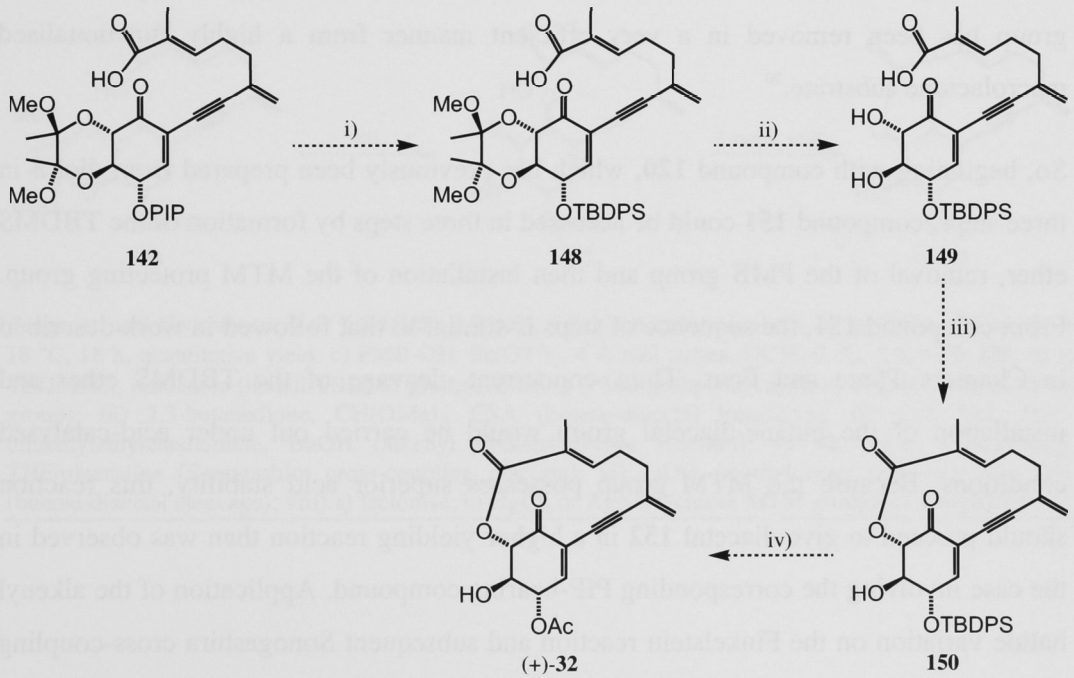
4.4.1 Preamble

Clearly the path being taken in the last few steps of the synthetic work described above is not a suitable one for obtaining (+)-tricholomenyn B. While time constraints have prevented further work (by the author) directed towards completion of the synthesis of (+)-tricholomenyn B, a number of possibilities exist for the successful realisation of this aim. The following sections outline two possible approaches, the first of which details minor modifications to the route described above. The second possible approach involves changes that could be made nearer the beginning of the synthesis and that also seek to deal with the low yields encountered when manipulating the butane-diacetal protecting group.

4.4.2 First possible approach to completing the synthesis of (+)-trichlomenyn B

The first possible approach to completing the synthesis of the target (+)-**32** involves replacing the PIP protecting group within compound **142** with one that is able to withstand the acidic conditions required to remove the diacetal moiety (Scheme 4.5). Accordingly, it should be possible to remove the PIP moiety under oxidative conditions and then protect the resulting hydroxyl group as the TBDPS ether so as to give compound **148**. The butane-diacetal moiety could then be removed using TFA in the presence of water* and the lactonisation step carried out to give compound **150**. Completion of the synthesis then requires removal of the TBDPS group from within this last compound and selective acetylation of the allylic alcohol so formed to give the final target (+)-**32**.

Scheme 4.5: *A proposed route for completing the synthesis of tricholomenyn B from compound* ***142***



Reagents and Conditions: i) a) DDQ (PMB group cleavage); b) TBDPSCl, imidazole (install TBDPS group); ii) TFA, DCM/H_2O (remove *bis*-acetal protecting group); iii) lactonise; iv) a) F- (TBDPS group cleavage); b) acetylation.

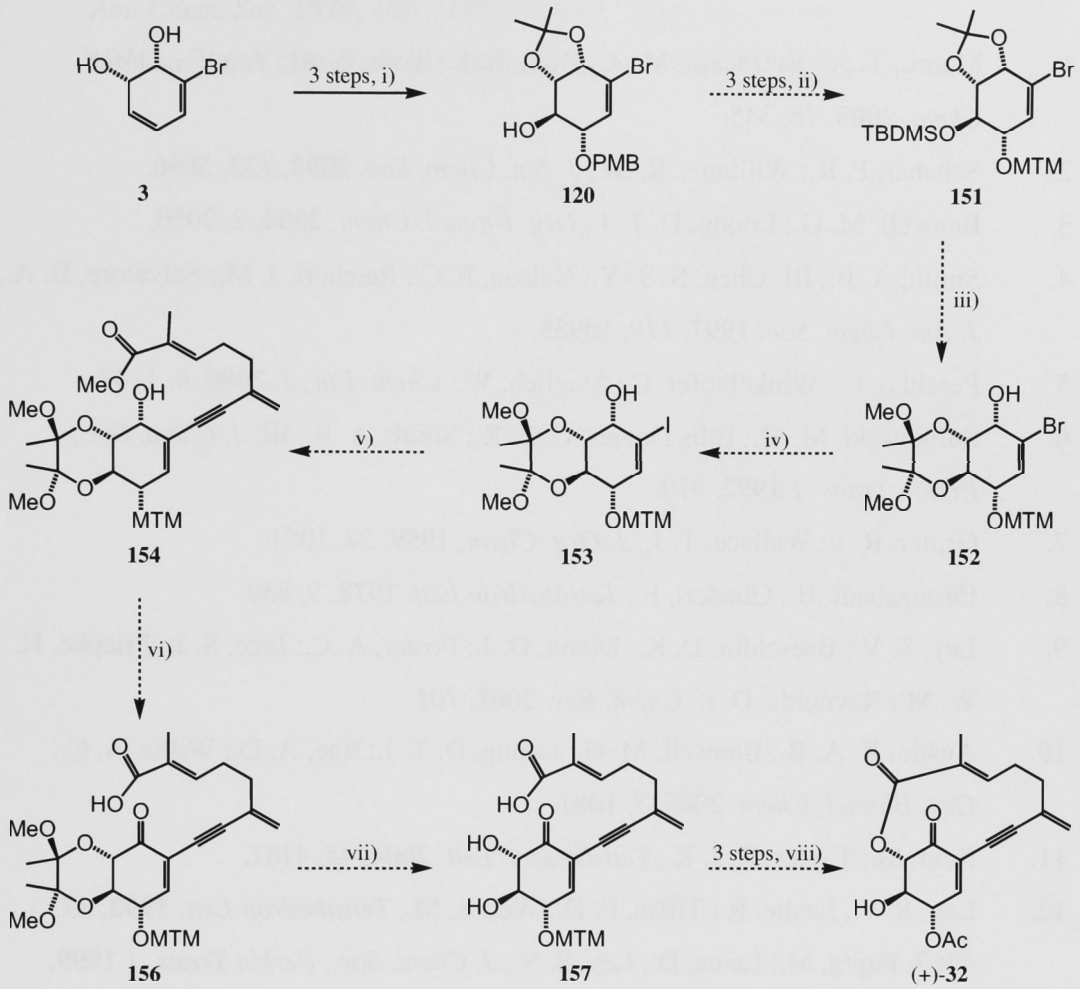
*There is literature precedent which indicates that a TBDPS-ether will withstand treatment with aqueous TFA [18].

4.4.3 Second possible approach to completing the synthesis of (+)-trichlomenyn B

The second approach to target (+)-**32** would be to incorporate the necessary protecting group changes at the early stages of the synthetic sequence, as is shown in Scheme 4.6. Given that the earlier studies described in this thesis resulted in complications arising from a TBDPS group undergoing a base-promoted migration, this unit is clearly not suited to incorporation into the synthetic sequence prior to the Sonogashira cross-coupling and methyl ester cleavage steps. In many respects the route laid out in Scheme 4.6 is similar to that already used, however it also features the use of a methylthiomethyl (MTM) alcohol protecting group in the location which was formerly occupied by the PIP or TBDPS moieties. The MTM group is the thiol equivalent of a MOM group, and has two distinct advantages in that it is very acid stable yet can be cleaved by heavy metal salts such as $HgCl_2$ or $AgNO_3$ and without affecting a lactone functionality.[19] Indeed, there are various examples in the literature where the MTM group has been removed in a very efficient manner from a highly functionalised macrolactone substrate.[20]

So, beginning with compound **120**, which has previously been prepared from diol **3** in three steps, compound **151** could be accessed in three steps by formation of the TBDMS ether, removal of the PMB group and then installation of the MTM protecting group. From compound **151**, the sequence of steps is similar to that followed in work described in Chapters Three and Four. Thus, concurrent cleavage of the TBDMS ether and installation of the butane-diacetal group would be carried out under acid-catalysed conditions. Because the MTM group possesses superior acid stability, this reaction should proceed to give diacetal **152** in a higher yielding reaction than was observed in the case involving the corresponding PIP-bearing compound. Application of the alkenyl halide variation on the Finkelstein reaction and subsequent Sonogashira cross-coupling of substrate **153** and alkyne **92** would then be expected to give compound **154**. Methyl ester and *bis*-acetal cleavage leading to compound **157** could then be followed by the lactonisation reaction and subsequent manipulations required to deliver the target compound (+)-tricholomenyn B.

***Scheme 4.6**: A second possible route to complete the synthesis of tricholomenyn B*



Reagents and Conditions: i) a) 2,2-DMP, *p*-TsOH, 1.5 h, quantitative yield; b) *m*-CPBA, DCM, 0 → 18 °C, 18 h, quantitative yield; c) PMB-OH, $Sc(OTf)_3$, 4 Å mol sieves, DCM, 0 °C, 3 h, 43% **120**; ii) a) TBDMSCl, imidazole (install TBDMS group); b) DDQ (PMB group cleavage); c) MTMCl (install MTM group); iii) 2,3-butanedione, $CH(OMe)_3$, CSA (butane-diacetal formation); iv) CuI, NaI, *N,N'*-dimethylethylenediamine, BuOH (alkenyl Finkelstein-type reaction); v) **92**, $InCl_3$, $PdCl_2(PPh_3)_2$, THF/piperidine (Sonogashira cross-coupling reaction); vi) LiOH (methyl ester removal); vii) TFA (butane-diacetal cleavage); viii) a) lactonise; b) $HgCl_2$ or $AgNO_3$ (cleave MTM group); c) acetylation.

4.5 REFERENCES

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EXPERIMENTAL PROCEDURES

5.1 GENERAL PROCEDURES

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 20 °C in $CDCl_3$ or CD_3OD on a Varian Inova 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. In certain cases, a Varian Inova 600 spectrometer operating at 600 MHz for proton and 150 MHz for carbon nuclei was used. Signals arising from the residual protio-forms of the solvent were employed as the internal standard. ^{1}H NMR data are recorded as follows: chemical shift (δ) [relative integral, multiplicity, coupling constant(s) *J* (Hz)] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The central peak (δ 77.0) of the $CDCl_3$ triplet or the central peak (δ 49.0) of the CD_3OD septet was used to reference proton-decoupled ^{13}C NMR spectra. For ^{13}C NMR spectra the data are given as: chemical shift (δ), (protonicity), where protonicity is defined as: C = quaternary; CH = methine; CH_2 = methylene; CH_3 = methyl. Assignment of signals observed in various NMR spectra were often assisted by conducting distortionless enhancement of polarization transfer (DEPT), attached proton test (APT), homonuclear (^{1}H-^{1}H) correlation spectroscopy (COSY), heteronuclear single quantum correlation (HSQC) and/or nuclear Overhauser effect (NOE) experiments.

Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer 1800 Series FTIR Spectrometer. Samples were analysed as KBr disks (for powdery solids) or as thin films on NaCl plates (for oils and crystalline solids).

A VG Fisons AutoSpec three sector (E/B/E) double-focussing mass spectrometer was used to obtain low- and high-resolution electron impact (EI) mass spectra. Low- and high-resolution electrospray mass spectra were obtained on a VG Quattro II triple quadrupole MS instrument operating in either positive and/or negative ionisation modes.

Optical rotations were measured with a Perkin-Elmer 241 polarimeter at the sodium-D line (589 nm) and the concentrations (*c*) (g/100 mL) indicated, using spectroscopic grade $CHCl_3$ or HPLC grade MeOH as solvent. The measurements were carried out in a cell with a path length (l) of 1 dm. Specific rotations $[\alpha]_D$ were calculated (at 21 °C) using the equation $[\alpha]_D = 100.\alpha/(c.l)$ and are given in $10^{-1}.deg.cm^2.g^{-1}$.

Melting points were measured on a Stanford Research System "OptiMelt" apparatus.

Microwave experiments were carried out using a CEM Discover reactor.

Elemental analyses were performed by the Australian National University's Microanalytical Services Unit based at the Research School of Chemistry, Canberra, Australia.

Analytical thin layer chromatography (TLC) was performed on aluminium backed 0.2 mm thick silica gel 60 F254 plates as supplied by Merck. Eluted plates were visualised by treatment with a suitable dip followed by heating. These dips were composed of phosphomolybdic acid, ceric sulfate, sulfuric acid (conc.) and water (37.5 g : 7.5 g : 37.5 g : 720 mL), or vanillin, MeOH and sulfuric acid (conc.) (5 g : 500 mL : 25 mL). Flash chromatography was performed using the analytical grade solvents indicated and silica gel 60 (0.040 – 0.0063 mm) as supplied by Merck.

Room temperature is assumed to be *ca.* 18 °C.

Starting materials and reagents were generally available from the Sigma-Aldrich-Fluka (SAF), Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied or, in the case of some liquids, distilled. All *cis*-1,2-dihydrocatechols were generously provided by Dr G. Whited of Genencor International Inc. (Palo Alto, CA) or by Professor D. Boyd of the Queen's University, Belfast. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran (THF), dioxane, and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Methanol (MeOH) and ethanol (EtOH) were distilled from calcium oxide while dichloromethane (DCM) was distilled from calcium hydride. Hexane and ethyl acetate (EtOAc) were distilled without using drying reagents. Benzene was dried over sodium and used without distillation. Pyridine, triethylamine,

piperidine and diisopropylamine were all distilled from potassium hydroxide pellets and stored over activated 4 Å molecular sieves.

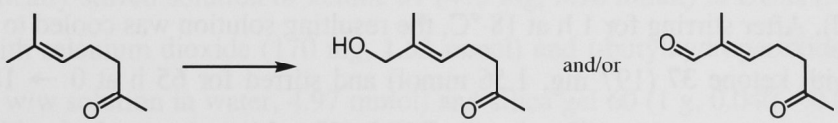
5.2 General Methods For the Preparation of Commercially Unavailable Reagents

Barium manganate was prepared according to the method of Firouzabadi *et al.*,[1] while dimethyldioxirane was generated using the protocol reported by Adam *et al.*[2] The Dess-Martin periodinane was prepared by the method of Santagostino *et al.*[3]

Diazomethane was prepared by the dropwise addition of a solution of Diazald™ (10.7 g, 0.05 mol) in Et_2O (*ca.* 60 mL) to a mixture of KOH (3 g), water (5 mL) and carbitol (diethyleneglycol monomethyl ether, 20 mL) that was maintained at 80 °C. The distilled ethereal diazomethane (*ca.* 0.034 mol) was collected in a conical flask containing potassium hydroxide, and stored at –18 °C before use. CAUTION: Diazomethane is a potential explosive and is also toxic. All glassware used was scratch-free and contained no ground-glass joints. The preparation of this reagent was carried out behind a blast shield. All waste was neutralised with HCl (0.5 M aqueous solution) before being disposed of in the appropriate manner.

5.3 Experimental Procedures Associated with Work Described in Chapter Two

(*E*)-7-Hydroxy-6-methylhept-5-en-2-one (73) and (*E*)-2-methyl-6-oxohept-2-enal (74)



37 **73** **74**

Method A

A magnetically stirred solution of ketone **37** (197 mg, 1.56 mmol) in dry dioxane/EtOH (5 mL of a 9:1 v/v mixture) maintained under a nitrogen atmosphere was treated with selenium dioxide (202 mg, 1.82 mmol). The resulting mixture was heated at 80 °C for

4.5 h, then cooled, diluted with DCM (20 mL) and washed with water (1 x 20 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting orange oil was subjected to flash chromatography (silica, 5:1 → 2:1 v/v hexane/EtOAc gradient elution) and concentration of the appropriate fractions (R_f 0.2 in 2:1 v/v hexane/EtOAc) afforded the previously reported keto-aldehyde **74**[4-7] (74 mg, 34%) as a pale-orange oil and thus indicating that it was contaminated with selenium residues.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (1H, s), 6.41 (1H, m), 2.68 – 2.52 (4H, complex m), 2.15 (3H, s), 1.72 (3H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7 (C), 194.9 (CH), 152.5 (CH), 139.6 (C), 41.4 (CH_2), 29.7 (CH_3), 22.7 (CH_2), 8.9 (CH_3)

IR (thin film) ν_{max} 2978, 2931, 1717, 1685, 1645, 1363, 1161, 1048, 873 cm^{-1}

EIMS (70 eV) *m/z* 140 ($M^{+\bullet}$, <1%), 122 (17), 112 (28), 97 (100)

HRMS (EI) Found: $M^{+\bullet}$, 140.0838. $C_8H_{12}O_2$ requires $M^{+\bullet}$, 140.0837

The spectroscopic data obtained on the material prepared as described above were in good agreement with those reported previously for compound **74**.[4,5,7]

Method B

A magnetically stirred solution of selenium dioxide (19 mg, 0.17 mmol) in DCM (3 mL) maintained under a nitrogen atmosphere was treated with salicylic acid (23 mg, 0.17 mmol) and *t*-butylhydroperoxide (1.1 mL of a 5.0 M solution in decane, 5.6 mmol). After stirring for 1 h at 18 °C, the resulting solution was cooled to 0 °C then treated with ketone **37** (197 mg, 1.56 mmol) and stirred for 65 h at 0 → 18 °C. The reaction mixture was then diluted with DCM (50 mL) and quenched with $Na_2S_2O_3$ (50 mL of a 20% w/v aqueous solution). The separated aqueous phase was extracted with DCM (1 x 50 mL) and the combined organic phases were washed with water (1 x 100 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting orange oil was subjected to flash chromatography (silica, 5:1 → 2:1 v/v hexane/EtOAc gradient elution) to afford two fractions, A and B.

Concentration of the fraction A (R_f 0.2 in 2:1 v/v hexane/EtOAc) afforded the previously reported keto-aldehyde **74**[4-7] (70 mg, 32%) as a pale-orange oil and thus indicating that it was contaminated with selenium residues. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **47** prepared by Method A.

Concentration of the fraction B (R_f 0.1 in 2:1 v/v hexane/EtOAc) afforded the previously reported keto-alcohol **73**[5,6] (40 mg, 18%) as a pale-orange oil and thus indicating that it was contaminated with selenium residues.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (1H, tq, *J* 7.1 and 1.4 Hz), 3.98 (2H, s), 2.50 (2H, m), 2.31 (2H, m), 2.14 (3H, s), 1.67 (3H, s), (signal due to the hydroxyl proton was not observed)

^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2 (C), 136.2 (C), 124.2 (CH), 68.6 (CH_2), 43.2 (CH_2), 29.7 (CH_3), 21.9 (CH_2), 13.6 (CH_3)

IR (thin film) ν_{max} 3415, 2923, 2854, 1713, 1455, 1360, 1160, 1013 cm^{-1}

ESI-MS (70 eV) *m/z* 165 [$(M + Na)^+$, 100%]

HRMS (ESI) Found: $(M + Na)^+$, 165.0897. $C_8H_{14}O_2$ requires $(M + Na)^+$, 165.0891

The spectroscopic data obtained on the material prepared as described above were in good agreement with those reported previously for compound **73**.[4,5]

Method C

A magnetically stirred solution of ketone **37** (402 mg, 3.18 mmol) in DCM (5 mL) was treated with selenium dioxide (170 mg, 1.53 mmol) and *t*-butylhydroperoxide (639 mg of a 70% w/w solution in water, 4.97 mmol) and silica gel 60 (1 g, 0.040 – 0.0063 mm, chromatography grade). The resulting slurry was concentrated under reduced pressure to give a free-flowing powder. This material was subjected to microwave irradiation at 150 W for 0.4 h then Et_2O (10 mL) was added to the cooled material and the ensuing mixture filtered. The solids thus retained were washed with Et_2O (100 mL) and the combined filtrates were cooled to 0 °C then treated, over 0.5 h, with $Na_2S_2O_5$ (100 mL of a 20% w/v aqueous solution). The separated aqueous phase was extracted with DCM

(1 x 100 mL) and the combined organic phases washed with $NaHCO_3$ (1 x 100 mL of a saturated aqueous solution) and brine (1 x 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting orange oil was subjected to flash chromatography (silica, 5:1 → 2:1 v/v hexane/EtOAc gradient elution) and concentration of the appropriate fractions (R_f 0.2 in 2:1 v/v hexane/EtOAc) afforded the previously reported keto-aldehyde **74**[4-7] (214 mg, 48%) as a pale-orange oil and thus indicating that it was contaminated with selenium residues.

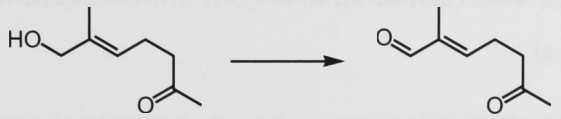
The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **47** prepared by Method A.

Method D

Selenium dioxide (557 mg, 5.02 mmol) was added to a magnetically stirred suspension of silica gel 60 (9.2 g, 0.040 – 0.0063 mm, chromatography grade) in EtOH/water (60 mL of a 5:1 v/v mixture) and the resulting mixture concentrated on a rotary evaporator until a free-flowing powder was obtained. DCM (30 mL) then *t*-butylhydroperoxide (2.5 mL of a 5.0 – 6.0 M solution in nonane, 12.5 – 15.0 mmol) were added to this powder and the resulting slurry treated with ketone **37** (1.28 g, 10.2 mmol). The ensuing mixture was stirred at 18 °C for 48 h, then filtered through a sintered-glass funnel. The solids thus retained were washed with DCM (200 mL) and the combined filtrates cooled to 0 °C then treated, over 0.5 h, with $Na_2S_2O_5$ (100 mL of a 20% w/v aqueous solution). The separated aqueous phase was extracted with DCM (3 x 100 mL) and the combined organic phases washed with $NaHCO_3$ (1 x 100 mL of a saturated aqueous solution) and brine (1 x 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 5:1 → 2:1 v/v hexane/EtOAc gradient elution) and concentration of the appropriate fractions (R_f 0.2 in 2:1 v/v hexane/EtOAc) afforded the previously reported keto-aldehyde **74**[4-7] (695 mg, 49%) as a pale-yellow oil.

The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **47** prepared by Method A.

(*E*)-2-Methyl-6-oxohept-2-enal (74)

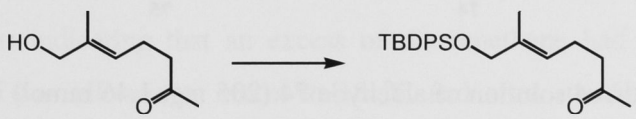


73 **74**

A magnetically stirred solution of alcohol **73** (1.08 g, 7.55 mmol) in Et_2O (30 mL) maintained at 18 °C under a nitrogen atmosphere was treated with MnO_2 (5.81 g, 66.8 mmol). The resulting slurry was stirred for 20 h before being filtered through a short plug of Celite™. Concentration of the filtrate under reduced pressure afforded a dark-yellow oil that was subjected to flash chromatography (silica, 5:1 → 1:1 hexane/EtOAc gradient elution). Concentration of the appropriate fractions (R_f 0.2 in 2:1 v/v hexane/EtOAc) then gave the previously reported keto-aldehyde **74**[4-7] (650 mg, 61%) as a pale-yellow oil.

The spectral data derived from this material were in good agreement with those obtained from the sample of compound **74** prepared as described on page 91.

***tert*-Butyl-{7-[(*E*)-6-methylhept-5-en-2-oxo]}diphenylsilane (86)**



73 **86**

A magnetically stirred solution of alcohol **73** (40 mg, 0.28 mmol) in DCM (0.3 mL) maintained under a nitrogen atmosphere was treated with imidazole (59 mg, 0.87 mmol) and *t*-butyldiphenylchlorosilane (85 mg, 0.31 mmol). The resulting mixture was stirred at 18 °C for 18 h then diluted with DCM (10 mL) and washed with water (1 x 10 mL). The separated organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting pale-yellow oil was subjected to flash chromatography (silica, 20:1 → 5:1 v/v hexane/EtOAc gradient elution) and concentration of the relevant fractions (R_f 0.5 in 10:1 v/v hexane/EtOAc) afforded the *title compound* ***86*** (102 mg, 95%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (4H, m), 7.46 – 7.36 (6H, complex m), 5.41 (1H, tq, *J* 7.1 and 1.4 Hz), 4.05 (2H, br s), 2.48 (2H, m), 2.32 (2H, m), 2.15 (3H, s), 1.62 (3H, br s), 1.08 (9H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8 (C), 135.5 (4 x CH), 135.2 (2 x C), 133.8 (C), 129.6 (2 x CH), 127.6 (4 x CH), 122.3 (CH), 68.7 (CH_2), 43.5 (CH_2), 30.0 (CH_3), 26.8 (3 x CH_3), 21.9 (CH_2), 19.3 (C), 13.4 (CH_3)

IR (thin film) ν_{max} 3071, 2930, 2857, 1959, 1888, 1822, 1705, 1589, 1472, 1427, 1361, 1111, 820 cm^{-1}

EIMS (70 eV) *m/z* 380 ($M^{+\bullet}$, <1%), 323 [$(M - C_4H_9\bullet)^+$, 68%], 267 (31), 239 (63), 199 (100), 181 (11), 139 (23), 105 (23), 77 (17)

HRMS (EI) Found: $(M - C_4H_9\bullet)^+$, 323.1492. $C_{24}H_{32}O_2Si$ requires $(M - C_4H_9\bullet)^+$, 323.1467

(*E*)-2-Methyl-6-oxohept-2-enoic acid (75)

74 **75**

A magnetically stirred solution of aldehyde **74** (205 mg, 1.46 mmol) in *t*-BuOH (8 mL) and water (2 mL) was treated with 2-methyl-2-butene (1.5 mL of a 2.0 M solution in THF, 3.0 mmol) and sodium dihydrogen phosphate monohydrate (244 mg, 1.56 mmol). After stirring at 18 °C for 0.2 h, the resulting solution was cooled to 0 °C and treated with sodium chlorite (384 mg, 4.25 mmol). The reaction mixture was stirred for 20 h at 0 → 18 °C then quenched with HCl (6 mL of a 0.5 M aqueous solution) and extracted with DCM (4 x 25 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting clear, colourless oil was subjected to flash chromatography (silica, 2:1 → 1:1 v/v hexane/EtOAc gradient elution) and concentration of the appropriate fractions (R_f 0.2 in 1:1 v/v hexane/EtOAc) then afforded the *title keto-acid* ***75*** (198 mg, 87%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (1H, m), 2.60 (2H, t, *J* 6.9 Hz), 2.46 (2H, t, *J* 6.9 Hz), 2.16 (3H, s), 1.85 (3H, broad s) (signal due to the carboxylic acid proton was not observed)

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3 (C), 173.2 (C), 142.9 (CH), 128.0 (C), 41.8 (CH_2), 29.9 (CH_3), 22.9 (CH_2), 12.0 (CH_3)

IR (thin film) ν_{max} 3414, 2930, 1711, 1689, 1644, 1417, 1363, 1282, 1166 cm^{-1}

EIMS (70 eV) *m/z* 156 ($M^{+\bullet}$, 1%), 155 (3), 154 (5), 138 (41), 95 (77), 43 (100)

HRMS (EI) Found: $M^{+\bullet}$, 156.0783. $C_8H_{12}O_3$ requires $M^{+\bullet}$, 156.0786

Methyl (*E*)-2-methyl-6-oxohept-2-enoate (76)

75 **76**

A solution of carboxylic acid **75** (84 mg, 0.54 mmol) in Et_2O (3 mL) was cooled to *ca.* – 10 °C then treated with diazomethane (*ca.* 0.57 M in Et_2O) until a bright-yellow colour persisted and thus indicating that an excess of diazomethane had been added. The resulting mixture was allowed to warm to 18 °C and after standing for 2 h it was concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 5:1 v/v hexane/EtOAc elution) and concentration of the appropriate fractions (R_f 0.15 in 5:1 v/v hexane/EtOAc) afforded the previously reported keto-ester **76**[8] (87 mg, 95%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (1H, tq, *J* 7.2 and 1.5 Hz), 3.68 (3H, s), 2.55 (2H, t, *J* 7.2 Hz), 2.40 (2H, m), 2.12 (3H, s), 1.81 (3H, broad s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3 (C), 168.4 (C), 140.3 (CH), 128.5 (C), 51.7 (CH_3), 42.0 (CH_2), 29.9 (CH_3), 22.6 (CH_2), 12.3 (CH_3)

IR (thin film) ν_{max} 2953, 1714, 1650, 1436, 1268, 1123, 746 cm^{-1}

EIMS (70 eV) *m/z* 170 ($M^{+\bullet}$, 1%), 138 (67), 95 (100)

HRMS (EI) Found: $M^{+\bullet}$, 170.0940. $C_9H_{14}O_3$ requires $M^{+\bullet}$, 170.0943

Elemental Analysis Found: C, 63.32; H, 7.98. $C_9H_{14}O_3$ requires C, 63.51; H, 8.29%

The spectroscopic data obtained on the material prepared as described above were in good agreement with those reported previously for compound **76**.[8]

(±)-2,6-Dimethyl-2-cyclohexen-1-one (81)

80 **81**

A magnetically stirred solution of ketone **80** (4.44 g, 35.2 mmol) in 1,2-dichloroethane (30 mL) was heated at reflux then treated with *N*-bromosuccinimide (6.94 g, 39.0 mmol) and AIBN (71 mg, 0.43 mmol). After a further 4.75 h, the reaction mixture was cooled to 18 °C, then diluted with Et_2O (30 mL) and quenched with $Na_2S_2O_3$ (1 x 50 mL of a 5% w/v aqueous solution). The separated organic phase was washed with $NaHCO_3$ (1 x 50 mL of a saturated aqueous solution) and brine (1 x 50 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 50:1 → 10:1 v/v hexane/EtOAc gradient elution) and concentration of the appropriate fractions (R_f 0.35 in 10:1 v/v hexane/EtOAc) afforded the previously reported (±)-2,6-dimethyl-2-cyclohexen-1-one (**81**)[9,10] (2.60 g, 60%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (1H, m), 2.34 – 2.20 (3H, complex m), 1.94 (1H, m), 1.66 (3H, dd, *J* 3.2 and 1.7 Hz), 1.60 (1H, m), 1.03 (3H, d, *J* 6.7 Hz)

^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2 (C), 144.4 (CH), 134.7 (C), 41.4 (CH), 31.1 (CH_2), 25.1 (CH_2), 15.9 (CH_3), 15.0 (CH_3)

IR (thin film) ν_{max} 2963, 2928, 1672, 1455, 1375, 1115, 995, 883 cm^{-1}

EIMS (70 eV) *m/z* 124 ($M^{+\bullet}$, 39%), 82 (100), 54 (30)

HRMS (EI) Found: $M^{+\bullet}$, 124.0898. $C_8H_{12}O$ requires $M^{+\bullet}$, 124.0888

The spectroscopic data obtained on the material prepared as described above were in good agreement with those reported previously for compound **81**.[10]

(±)-6-Hydroxy-2,6-dimethylcyclohex-2-enone (82)

81 **82**

A solution of enone **81** (2.49 g, 20.1 mmol) in THF (55 mL) was added to a magnetically stirred solution of potassium hexamethyldisilazide (44.3 mL of an 0.5 M solution in toluene, 22.2 mmol) in THF (90 mL) maintained at –78 °C under a nitrogen atmosphere. After 0.75 h the now bright-orange mixture was treated with a solution of 3-phenyl-2-phenylsulfonyl oxaziridine (9.06 g, 34.3 mmol) in THF (30 mL). The resulting mixture was stirred at –78 °C for 1 h then quenched with NH_4Cl (25 mL of a saturated aqueous solution) and warmed to 18 °C. The separated aqueous phase was extracted with Et_2O (3 x 100 mL) and the combined organic phases washed with brine (1 x 300 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 5:1 v/v hexane/EtOAc elution) and concentration of the appropriate fractions (R_f 0.3 in 5:1 v/v hexane/EtOAc) afforded the *title acyloin* ***82*** (1.86 g, 66%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (1H, m), 3.75 (1H, broad s, -O*H*), 2.29 (2H, m), 2.03 – 1.85 (2H, complex m), 1.68 (3H, dd, *J* 3.4 and 1.9 Hz), 1.18 (3H, s)

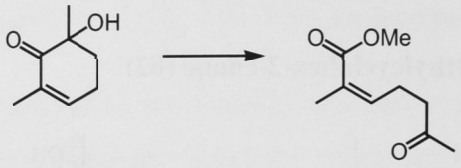
^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9 (C), 145.3 (CH), 132.3 (CH), 72.8 (CH), 35.5 (CH_2), 24.1 (CH_3), 23.8 (CH_2), 15.5 (CH_3)

IR (thin film) ν_{max} 3489, 2974, 2929, 1671, 1357, 1341, 1197, 1151, 1099, 1028, 983, 883 cm^{-1}

EIMS (70 eV) *m/z* 140 ($M^{+\bullet}$, <1%), 112 (61), 82 (100), 54 (32)

HRMS (EI) Found: $M^{+\bullet}$, 140.0839. $C_8H_{12}O_2$ requires $M^{+\bullet}$, 140.0837

Methyl (*Z*)-2-methyl-6-oxohept-2-enoate (77)



82 **77**

A magnetically stirred solution of acyloin **82** (965 mg, 6.87 mmol) in MeOH (13 mL) was treated with a solution of lead tetra-acetate (6.06 g, 13.7 mmol) in benzene (55 mL) and the resulting mixture heated at 40 °C for 3 h. The cooled reaction mixture was diluted with water (70 mL) and Et_2O (70 mL) then the separated aqueous phase was extracted with DCM (1 x 100 mL) then Et_2O (1 x 100 mL). The combined organic phases were washed with $NaHCO_3$ (1 x 100 mL of a saturated aqueous solution) and brine (1 x 100 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 5:1 v/v hexane/EtOAc elution) and concentration of the appropriate fractions (R_f 0.4 in 5:1 v/v hexane/EtOAc) afforded the previously reported keto-ester **77**[11] (980 mg, 84%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (1H, m), 3.61 (3H, s), 2.56 (2H, m), 2.45 (2H, m), 2.02 (3H, s), 1.75 (3H, d, *J* 1.2 Hz)

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6 (C), 167.8 (C), 141.0 (CH), 127.6 (C), 51.0 (CH_3), 42.7 (CH_2), 29.4 (CH_3), 23.6 (CH_2), 20.2 (CH_3)

IR (thin film) ν_{max} 2954, 1712, 1646, 1456, 1436, 1365, 1241, 1129, 1052, 770 cm^{-1}

EIMS (70 eV) *m/z* 170 ($M^{+\bullet}$, 1%), 138 (71), 127 (28), 95 (100), 67 (45)

HRMS (EI) Found: $M^{+\bullet}$, 170.0941. $C_9H_{14}O_3$ requires $M^{+\bullet}$, 170.0943

Elemental Analysis Found: C, 63.65; H, 8.62. $C_9H_{14}O_3$ requires C, 63.51; H, 8.29%

The spectroscopic data obtained on the material prepared as described above were in good agreement with those reported previously for compound **77**.[11]

6-Methylhepta-1,5-dien-2-yl trifluoromethanesulfonate (38)

37 **38**

A magnetically stirred solution of diisopropylamine (2.06 g, 22.5 mmol) in THF (20 mL) maintained at –10 °C under a nitrogen atmosphere was treated with *n*-butyllithium (12.7 mL of a 1.6 M solution in hexanes, 20.3 mmol). After 0.25 h the solution was warmed to 18 °C for 0.25 h then cooled to –78 °C before being treated, dropwise, with ketone **37** (1.97 g, 15.6 mmol). Stirring was continued for 1 h, then *N*-phenyl-*bis*-triflimide (5.93 g, 16.6 mmol) was added to the reaction mixture. The resulting mixture was stirred for a further 20 h, during which time the reaction was allowed to warm to 18 °C. The reaction mixture was then diluted with DCM (50 mL) and washed with water (1 x 100 mL) and brine (1 x 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting brown oil was subjected to flash chromatography (hexane elution) to give two fractions, A and B.

Concentration of fraction A (R_f 0.7 in 5:1 v/v hexane/EtOAc) afforded starting material **37** (267 mg, 14% recovery). The spectral data obtained on this material were in good agreement with those published by the commercial supplier of compound **37**.[12]

Concentration of fraction B (R_f 0.7 in 10:1 v/v hexane/EtOAc) afforded the previously reported vinyl triflate **38**[13,14] [2.94 g, 73% (85% at 86% conversion)] as a clear, colourless oil that rapidly developed a brown tinge on warming or on prolonged storage at any temperature.

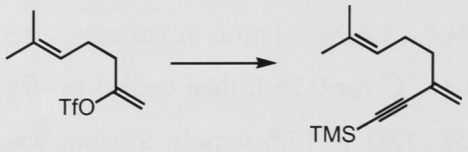
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (1H, d, *J* 3.4 Hz), 5.08 – 5.05 (1H, complex m), 4.93 (1H, dt, *J* 3.4 and 1.1 Hz), 2.39 – 2.34 (2H, complex m), 2.27 – 2.20 (2H, complex m), 1.70 (3H, d, *J* 1.1 Hz), 1.62 (3H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6 (C), 133.7 (C), 121.5 (CH), 104.3 (CH), 33.9 (CH_2), 25.6 (CH_2), 24.6 (CH_3), 17.6 (CH_3) (signal due to the CF_3 carbon was not observed)

IR (thin film) ν_{max} 2974, 2921, 2862, 1671, 1419, 1211, 1146, 942, 899, 604 cm^{-1}

This compound did not display a molecular ion or any logical fragment ions under a variety of mass spectrometric conditions. The remaining spectroscopic data obtained on the material prepared as described above were in good agreement with those reported previously for compound **38**.[13]

Trimethyl(7-methyl-3-methyleneoct-6-en-1-yn-1-yl)silane (45)



38 **45**

A magnetically stirred solution of vinyl triflate **38** (1.62 g, 6.31 mmol) in THF (20 mL) and piperidine (10 mL) maintained at 18 °C under a nitrogen atmosphere was treated with cuprous iodide (47 mg, 0.25 mmol) and dichloro*bis*(acetonitrile)palladium (30 mg, 0.12 mmol). The resulting yellow-green solution was treated with trimethylsilylacetylene (904 mg, 9.12 mmol) over a period of 0.3 h and stirred for a further for 0.25 h, after which time the reaction was judged to be complete as evidenced by the formation of palladium black. Accordingly, the reaction mixture was quenched with HCl (50 mL of a 0.5 M aqueous solution) then extracted with DCM (2 x 50 mL). The combined organic phases were washed with $NaHCO_3$ (1 x 100 mL of a saturated aqueous solution) and brine (1 x 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting bright-yellow oil was subjected to flash chromatography (silica, hexane elution) and concentration of the relevant fractions (R_f 0.75 in hexane) furnished the previously reported enyne **45**[13,14] (1.28 g, 97%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (1H, m), 5.24 (1H, m), 5.14 – 5.08 (1H, complex m), 2.25 – 2.12 (4H, complex m), 1.69 (3H, m), 1.63 (3H, m), 0.19 (9H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 132.2 (C), 131.4 (C), 123.3 (CH), 122.0 (CH_2), 105.4 (C), 93.9 (C), 37.3 (CH_2), 26.7 (CH_2), 25.7 (CH_3), 17.7 (CH_3), –0.1 (3 x CH_3)

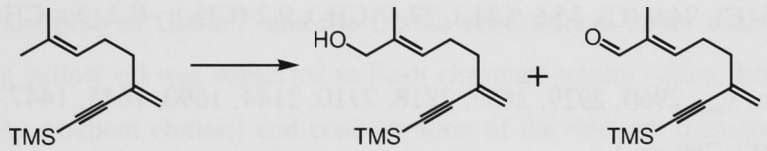
IR (thin film) ν_{max} 3095, 2963, 2927, 2857, 2145, 1606, 1449, 1376, 1250, 883, 842, 759 cm^{-1}

EIMS (70 eV) *m/z* 206 ($M^{+\bullet}$, 6%), 205 [$(M - H\bullet)^+$, 22%], 149 (15), 97 (24), 73 (100)

HRMS (EI) Found: $(M - H\bullet)^+$, 205.1413. $C_{13}H_{22}Si$ requires $(M - H\bullet)^+$, 205.1413

The spectroscopic data obtained on the material prepared as described above were in good agreement with those reported previously for compound **45**.[13]

(*E*)-2-Methyl-6-methylene-8-(trimethylsilyl)oct-2-en-7-yn-1-ol (88) and (*E*)-2-methyl-6-methylene-8-(trimethylsilyl)oct-2-en-7-ynal (89)



45 **88** **89**

Silica gel 60 (0.9 g, 0.040 – 0.0063 mm, chromatography grade) was added to a magnetically stirred solution of selenium dioxide (53 mg, 0.48 mmol) in EtOH/water (6 mL of a 5:1 v/v mixture) and the resulting mixture concentrated on a rotary evaporator until a free-flowing powder was obtained. DCM (40 mL) and *t*-butylhydroperoxide (1.6 mL of a 5.0 – 6.0 M solution in decane, 8.0 – 9.6 mmol) were added to this powder and the resulting slurry treated with alkene **45** (844 mg, 4.09 mmol) then stirred at 18 °C for 72 h. The ensuing mixture was filtered through a sintered-glass funnel and the solids thus retained were washed with DCM (200 mL). The combined filtrates were cooled to 0 °C then treated, over 0.5 h, with $Na_2S_2O_5$ (150 mL of a 20% w/v aqueous solution). The separated aqueous phase was extracted with DCM (3 x 100 mL) and the combined organic phases were washed with $NaHCO_3$ (1 x 150 mL of a saturated aqueous solution) and brine (1 x 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 20:1 → 5:1 v/v hexane/EtOAc gradient elution) to give three fractions, A, B and C.

Concentration of fraction A (R_f 0.8 in hexane) afforded starting material **45** (52 mg, 6% recovery). The spectroscopic data obtained on this material were in good agreement with those recorded earlier for compound **45**.

Concentration of fraction B (R_f 0.55 in 10:1 hexane/EtOAc) afforded *aldehyde **89*** (246 mg, 32%) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (1H, s), 6.47 (1H, tq, *J* 7.3 and 1.4 Hz), 5.41 (1H, m), 5.29 (1H, m), 2.60 (2H, q, *J* 7.3 Hz), 2.35 (2H, t, *J* 7.3 Hz), 1.77 (3H, m), 0.19 (9H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1 (C), 153.0 (CH), 139.8 (C), 130.0 (C), 122.9 (CH_2), 104.6 (C), 94.9 (C), 35.6 (CH_2), 27.4 (CH_2), 9.2 (CH_3), –0.2 (3 x CH_3)

IR (thin film) ν_{max} 2960, 2929, 2857, 2818, 2710, 2144, 1690, 1645, 1447, 1405, 1363, 1250, 886, 843, 760 cm^{-1}

EIMS (70 eV) *m/z* 220 ($M^{+\bullet}$, 15%), 219 [$(M - H\bullet)^+$, 26%], 205 (24), 163 (23), 147 (35), 131 (22), 97 (35), 75 (53), 73 (100)

HRMS (EI) Found: $M^{+\bullet}$, 220.1283. $C_{13}H_{20}OSi$ requires $M^{+\bullet}$, 220.1283

Concentration of fraction C (R_f 0.2 in 10:1 hexane/EtOAc) afforded *alcohol **88*** (179 mg, 20%) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (1H, m), 5.35 (1H, d, *J* 1.8 Hz), 5.23 (1H, m), 3.98 (2H, broad s), 2.28 – 2.16 (4H, complex m), 1.67 (3H, broad s), 0.17 (9H, s) (signal due to the hydroxyl proton was not observed)

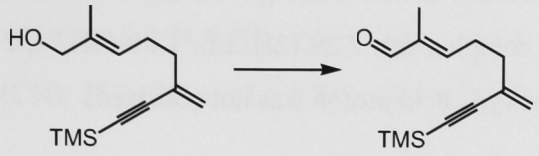
^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4 (C), 131.0 (C), 124.6 (CH), 122.0 (CH_2), 105.3 (C), 93.9 (C), 68.4 (CH_2), 36.7 (CH_2), 26.0 (CH_2), 13.5 (CH_3), –0.2 (3 x CH_3)

IR (thin film) ν_{max} 3369, 2960, 2143, 1676, 1607, 1454, 1364, 1250, 1005, 841, 759 cm^{-1}

EIMS (70 eV) *m/z* 222 ($M^{+\bullet}$, 24%), 207 (34), 204 (25), 191 (41), 164 (54), 132 (41), 123 (38), 117 (57), 97 (73), 75 (93), 73 (95), 43 (100)

HRMS (EI) Found: $M^{+\bullet}$, 222.1443. $C_{13}H_{22}OSi$ requires $M^{+\bullet}$, 222.1440

(*E*)-2-Methyl-6-methylene-8-(trimethylsilyl)oct-2-en-7-ynal (89)

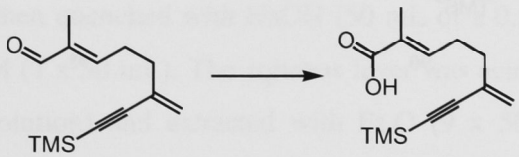


88 **89**

A magnetically stirred solution of alcohol **88** (174 mg, 0.78 mmol) in Et_2O (5 mL) maintained under a nitrogen atmosphere was treated with MnO_2 (1.33 g, 15.3 mmol) and the resulting slurry was stirred at 18 °C for 22 h. The ensuing mixture was filtered through a short plug of Celite™ and the filtrate concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, hexane → 20:1 hexane/EtOAc gradient elution) and concentration of the relevant fractions (R_f 0.55 in 10:1 hexane/EtOAc) afforded the *title aldehyde* ***89*** *(*114 mg, 66%) as a yellow oil.

The spectral data derived from this material were in good agreement with those obtained from the sample of compound **89** prepared as described on page 103.

(*E*)-2-Methyl-6-methylene-8-(trimethylsilyl)oct-2-en-7-ynoic acid (90)



89 **90**

A magnetically stirred solution of aldehyde **89** (938 mg, 4.25 mmol) in *t*-BuOH (28 mL) and water (7 mL) was treated with 2-methyl-2-butene (4.66 mL of a 2.0 M solution in THF, 9.20 mmol) followed by sodium dihydrogen phosphate monohydrate (760 mg, 4.87 mmol). After stirring at 18 °C for 0.2 h, the reaction mixture was cooled to 0 °C then treated with sodium chlorite (869 mg, 9.61 mmol). The resulting solution was stirred for 20 h at 0 → 18 °C, then quenched with HCl (50 mL of a 0.5 M aqueous solution) and extracted with DCM (3 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, colourless oil that was subjected to flash chromatography (silica, 10:1 v/v

hexane/EtOAc elution). Concentration of the appropriate fractions (R_f 0.3 in 10:1 hexane/EtOAc) afforded the *title keto-acid* ***90*** (836 mg, 83%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (1H, tq, *J* 7.3 and 1.4 Hz), 5.40 (1H, m), 5.27 (1H, m), 2.49 – 2.41 (2H, complex m), 2.29 (2H, m), 1.86 (3H, d, *J* 1.4 Hz), 0.19 (9H, s) (signal due to the carboxylic acid proton was not observed)

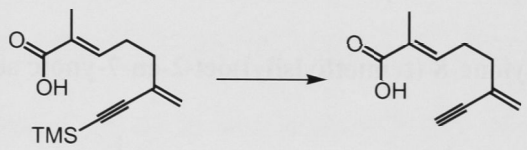
^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 (C), 143.7 (CH), 130.3 (C), 127.8 (C), 122.8 (CH_2), 104.8 (C), 94.7 (C), 35.8 (CH_2), 27.4 (CH_2), 12.0 (CH_3), –0.1 (3 x CH_3)

IR (thin film) ν_{max} 2960, 2901, 2665, 2551, 2146, 1689, 1644, 1609, 1421, 1286, 1251, 873, 843, 760 cm^{-1}

EIMS (70 eV) *m/z* 236 ($M^{+\bullet}$, 18%), 221 (39), 203 (16), 191 (15), 175 (22), 163 (64), 146 (33), 118 (47), 97 (44), 81 (35), 73 (100)

HRMS (EI) Found: $M^{+\bullet}$, 236.1235. $C_{13}H_{20}O_2Si$ requires $M^{+\bullet}$, 236.1233

(*E*)-2-Methyl-6-methyleneoct-2-en-7-ynoic acid (91)



90 **91**

Method A

A magnetically stirred solution of keto-acid **90** (357 mg, 1.51 mmol) in MeOH (4 mL) was treated with potassium carbonate (420 mg, 3.04 mmol). The resulting slurry was stirred at 18 °C for 16 h then quenched with HCl (20 mL of a 0.5 M aqueous solution) and extracted with DCM (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil that was subjected to flash chromatography (silica, 4:1 v/v hexane/EtOAc elution). Concentration of the appropriate fractions (R_f 0.4 in 5:1 v/v hexane/EtOAc) afforded the *title carboxylic acid* ***91*** (227 mg, 92%) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (1H, tq, *J* 1.4 and 7.3 Hz), 5.46 (1H, m), 5.34 (1H, m), 2.92 (1H, s), 2.45 – 2.42 (2H, complex m), 2.31 (2H, m), 1.86 (3H, s) (signal due to the carboxylic acid proton was not observed)

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7 (C), 143.5 (CH), 129.3 (C), 127.9 (C), 123.7 (CH_2), 83.4 (C), 77.6 (CH), 35.6 (CH_2), 27.3 (CH_2), 12.1 (CH_3)

IR (thin film) ν_{max} 3295, 2931, 2665, 2552, 1688, 1643, 1613, 1422, 1286, 1189, 909, 646 cm^{-1}

EIMS (70 eV) *m/z* 164 ($M^{+\bullet}$, 13%), 163 (24), 149 (29), 146 (41), 119 (85), 117 (52), 105 (39), 91 (88), 43 (100)

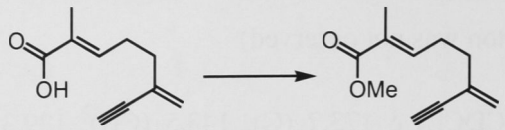
HRMS (EI) Found: $M^{+\bullet}$, 164.0837. $C_{10}H_{12}O_2$ requires $M^{+\bullet}$, 164.0837

Method B

A magnetically stirred solution of aldehyde **89** (779 mg, 3.53 mmol) in *t*-BuOH (32 mL) and water (8 mL) was treated with 2-methyl-2-butene (3.5 mL of a 2.0 M solution in THF, 7.0 mmol) followed by sodium dihydrogen phosphate monohydrate (505 mg, 3.68 mmol). After 0.2 h at 18 °C, the reaction mixture was cooled to 0 °C then treated with sodium chlorite (869 mg, 9.61 mmol). The resulting solution was stirred at 0 → 18 °C for 20 h, then quenched with NaOH (50 mL of a 0.5 M aqueous solution) and washed with DCM (1 x 50 mL). The aqueous layer was acidified to *ca.* pH 3 with HCl (2 M aqueous solution) and extracted with Et_2O (9 x 50 mL). The combined ethereal phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a colourless oil that was subjected to flash chromatography (silica, 10:1 → 5:1 v/v hexane/EtOAc, gradient elution). Concentration of the appropriate fractions (R_f 0.4 in 5:1 v/v hexane/EtOAc) afforded the *title carboxylic acid* ***91*** (379 mg, 65%) as a pale-yellow oil.

The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **91** prepared by Method A.

Methyl (*E*)-2-methyl-6-methyleneoct-2-en-7-ynoate (92)



91 **92**

A solution of carboxylic acid **91** (246 mg, 1.50 mmol) in Et_2O (10 mL) was cooled to *ca.* –10 °C then treated with diazomethane (*ca.* 0.57 M in Et_2O) until a bright-yellow colour persisted and thus indicating that an excess of diazomethane had been added. The resulting mixture was allowed to warm to 18 °C and after standing for 1 h was concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 10:1 → 2:1 v/v hexane/EtOAc gradient elution) and concentration of the appropriate fractions (R_f 0.6 in 10:1 v/v hexane/EtOAc) afforded the *title ester* ***92*** (252 mg, 95%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (1H, tq, *J* 7.2 and 1.4 Hz), 5.43 (1H, m), 5.31 (1H, m), 3.71 (3H, s), 2.91 (1H, s), 2.49 – 2.38 (2H, complex m), 2.28 (2H, m), 1.84 (3H, m)

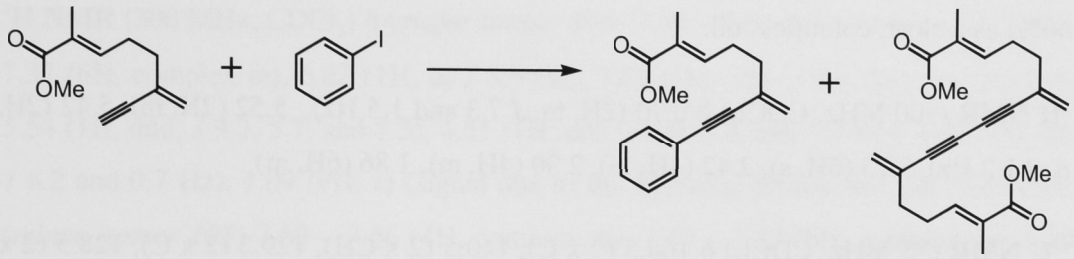
^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (C), 140.7 (CH), 129.4 (C), 128.2 (C), 123.4 (CH_2), 83.4 (C), 77.5 (CH), 51.6 (CH_3), 35.7 (CH_2), 27.0 (CH_2), 12.4 (CH_3)

IR (thin film) ν_{max} 3293, 2952, 2097, 1715, 1650, 1612, 1436, 1262, 1117, 1082, 908, 744, 612 cm^{-1}

EIMS (70 eV) *m/z* 178 ($M^{+\bullet}$, 13%), 177 [$(M - H\bullet)^+$, 94%], 163 (14), 149 (48), 145 (26), 119 (350), 117 (63), 91 (46), 73 (36), 59 (68), 57 (100)

HRMS (EI) Found: $(M - H\bullet)^+$, 177.0916. $C_{11}H_{14}O_2$ requires $(M - H\bullet)^+$, 177.0916

Methyl (*E*)-2-methyl-6-methylene-8-phenyloct-2-en-7-ynoate (94) and Dimethyl (2*E*,14*E*)-2,15-dimethyl-6,11-dimethylenehexadeca-2,14-dien-7,9-diynedioate (96)



92 **94** **96**

A magnetically stirred solution of iodobenzene (37 mg, 0.18 mmol) in THF (0.5 mL) maintained at 0 °C under a nitrogen atmosphere was treated sequentially with diisopropylamine (88 mg, 0.87 mmol), dichloro*bis*(triphenylphosphine)palladium (7 mg, 9.8 μmol) and cuprous iodide (4 mg, 22 μmol). The resulting mixture was then treated, dropwise, with a solution of alkyne **92** (32 mg, 0.18 mmol) in THF (1 mL). The ensuing green solution was stirred for an additional 2.5 h at 0 °C before being diluted with DCM (10 mL) and washed with water (1 x 10 mL). The separated organic phase was dried ($MgSO_4$), filtered then concentrated under reduced pressure and the resulting yellow oil was subjected to flash chromatography (silica, 10:1 v/v hexane/EtOAc elution) to afford two fractions, A and B.

Concentration of fraction A (R_f 0.5 in 10:1 v/v hexane/EtOAc) gave *cross-coupled product **94*** (18 mg, 38%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.41 (2H, complex m), 7.34 – 7.29 (3H, complex m), 6.79 (1H, td, *J* 7.1 and 1.4 Hz), 5.45 (1H, m), 5.31 (1H, m), 3.72 (3H, s), 2.48 (2H, m), 2.39 (2H, m), 1.88 (3H, m)

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7 (C), 141.2 (CH), 133.3 (2 x CH), 129.3 (C), 128.5 (C), 127.9 (2 x CH), 127.8 (CH), 125.2 (CH_2), 123.4 (C), 92.7 (C), 87.1 (C), 51.9 (CH_3), 35.6 (CH_2), 26.9 (CH_2), 12.3 (CH_3)

IR (thin film) ν_{max} 2927, 2856, 1721, 1461, 1271, 1120, 1073, 756, 691 cm^{-1}

EIMS (70 eV) *m/z* 254 ($M^{+\bullet}$, 11%), 253 [$(M - H\bullet)^+$, 33%], 239 (21), 195 (100), 179 (42), 167 (39), 149 (64), 115 (48), 77 (23)

HRMS (EI) Found: $(M - H\bullet)^+$, 253.1225. $C_{17}H_{18}O_2$ requires $(M - H\bullet)^+$, 253.1229.

Concentration of fraction B (R_f 0.3 in 10:1 v/v hexane/EtOAc) gave *dimer* ***96*** (7 mg, 46%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (2H, tq, *J* 7.3 and 1.5 Hz), 5.52 (2H, m), 5.42 (2H, d, *J* 1.2 Hz), 3.73 (6H, s), 2.42 (4H, m), 2.30 (4H, m), 1.86 (6H, m)

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5 (2 x C), 140.5 (2 x CH), 129.3 (2 x C), 128.5 (2 x C), 125.3 (2 x CH_2), 81.4 (2 x C), 73.9 (2 x C), 51.7 (2 x CH_3), 35.6 (2 x CH_2), 27.2 (2 x CH_2), 12.5 (2 x CH_3)

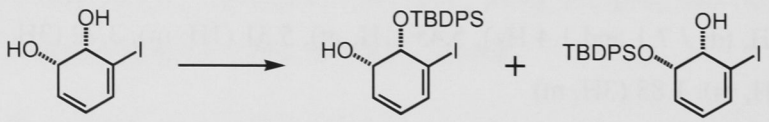
IR (thin film) ν_{max} 2950, 1715, 1651, 1435, 1270, 1192, 1121, 1081, 908, 745 cm^{-1}

EIMS (70 eV) *m/z* 354 ($M^{+\bullet}$, 10%), 339 (23), 307 (21), 295 (78), 279 (54), 263 (65), 235 (100), 219 (37), 207 (50), 193 (41), 181 (49), 165 (76), 152 (56), 141 (52), 128 (61), 115 (63)

HRMS (EI) Found: $M^{+\bullet}$, 354.1843. $C_{22}H_{26}O_4$ requires $M^{+\bullet}$, 354.1831

5.4 Experimental Procedures Associated with Work Described in Chapter Three

(1*S*,6*S*)-5-Iodo-6-(*tert*-butyldiphenylsiloxy)cyclohexa-2,4-dienol (105) and (1*S*,6*S*)-2-iodo-6-(*tert*-butyldiphenylsiloxy)cyclohexa-2,4-dienol (106)



104 **105** **106**

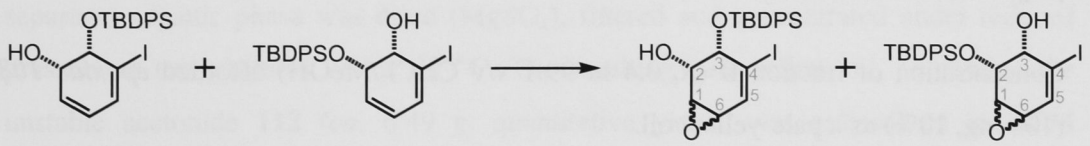
A magnetically stirred solution of diol **104** (508 mg, 2.14 mmol) in DCM (5 mL) maintained under a nitrogen atmosphere and protected from light was treated with imidazole (438 mg, 6.44 mmol) and *t*-butyldiphenylchlorosilane (634 mg, 2.31 mmol). After 1 h at 18 °C, the reaction mixture was diluted with Et_2O (15 mL) then washed with water (2 x 15 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure at temperatures below 25 °C. The resulting pale-yellow oil (1.02 g of a

5:1 mixture of *compounds* ***106*** and ***105***, quantitative yield) was immediately used, as obtained, in the next step of the reaction sequence.

^{1}H NMR (300 MHz, $CDCl_3$) δ (*major isomer* ***106***) 7.69 – 7.66 (4H, complex m), 7.49 – 7.37 (6H, complex m), 6.62 (1H, d, *J* 5.6 Hz), 5.65 (1H, ddd, *J* 9.7, 3.4, and 0.9 Hz), 5.54 (1H, ddd, *J* 9.7, 5.7, and 1.3), 4.51 (1H, ddd, *J* 6.0, 3.4, and 1.3 Hz), 4.08 (1H, dd, *J* 6.2 and 0.7 Hz), 1.09 (9H, s) (signal due to the hydroxyl proton was not observed); (*minor isomer* ***105***) 7.69 – 7.66 (4H, complex m), 7.49 – 7.37 (6H, complex m), 6.69 (1H, d, *J* 5.7 Hz), 5.88 (1H, ddd, *J* 9.5, 3.8, and 0.9 Hz), 5.71 (1H, ddd, *J* 9.5, 5.6, and 1.3), 4.35 (1H, dd, *J* 5.4 and 0.9 Hz), 3.98 (1H, ddd, *J* 5.3, 3.8, and 1.3 Hz), 1.09 (9H, s) (signal due to the hydroxyl proton was not observed)

^{13}C NMR (75 MHz, $CDCl_3$) δ (*major isomer* ***106***) 135.8 (2 x CH), 135.6 (2 x CH), 134.7 (CH), 133.1 (CH), 132.8 (CH), 130.2 (CH), 130.0 (CH), 129.2 (CH), 128.0 (2 x CH), 127.7 (2 x CH), 124.8 (CH), 102.1 (C), 74.2 (CH), 70.2 (CH), 26.9 (3 x CH_3), 19.3 (C)

(2*R*,3*S*)-4-Iodo-2-(*tert*-butyldiphenylsiloxy)-7-oxabicyclo[4.1.0]hept-4-en-3-ol (108) and (2*S*,3*S*)-4-iodo-3-(*tert*-butyldiphenylsiloxy)-7-oxabicyclo[4.1.0]hept-4-en-2-ol (107)



105 **106** **107** **108**

A magnetically stirred solution of compounds **106** and **105** (1.02 g of a 5:1 mixture, 2.14 mmol, obtained as described on the previous page) in DCM (35 mL), maintained at 0 °C under a nitrogen atmosphere and protected from the light, was treated with *m*-chloroperbenzoic acid (1.29 g of a 77% pure solid, 5.75 mmol). The resulting slurry was stirred for 16 h at 0 → 18 °C before being diluted with Et_2O (100 mL) then quenched with $Na_2S_2O_5$ (1 x 100 mL of a 20% w/v aqueous solution). The separated organic phase was washed with $NaHCO_3$ (1 x 100 mL of a saturated aqueous solution) and brine (1 x 100 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting orange oil was subjected to flash chromatography (silica, $CHCl_3$ elution) to give two fractions, A and B.

Concentration of fraction A (R_f 0.6 in 99:1 v/v $CHCl_3$/MeOH) afforded *epoxide* ***107*** (108 mg, 10%) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.67 (4H, complex m, Ar-*H*), 7.49 – 7.38 (6H, complex m, Ar-*H*), 6.86 (1H, dd, *J* 4.3 and 2.6 Hz, C5-*H*), 4.65 (1H, dd, *J* 4.9 and 2.9 Hz, C2-*H*), 3.94 (1H, ddd, *J* 11.5, 4.7 and 2.6 Hz, C3-*H*), 3.17 (1H, dd, *J* 3.7 and 2.9 Hz, C1-*H*), 3.00 (1H, t, *J* 4.1 Hz, C6-*H*), 2.72 (1H, d, *J* 11.5, -O*H*), 1.07 (9H, s, -CH_3)

^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8 (2 x CH), 135.6 (2 x CH), 133.4 (CH), 132.9 (C), 132.3 (C), 130.4 (CH), 130.3 (CH), 128.2 (2 x CH), 127.9 (2 x CH), 112.4 (C), 69.0 (CH), 68.7 (CH), 52.9 (CH), 49.4 (CH), 26.9 (3 x CH_3), 19.5 (C)

IR (thin film) ν_{max} 3552, 2930, 2857, 1610, 1471, 1427, 1362, 1240, 1112, 1029, 998, 889, 822, 741, 701 cm^{-1}

EIMS (70 eV) *m/z* 492 ($M^{+\bullet}$, 2%), 435 [$(M - C_4H_9\bullet)^+$, 53%], 417 (36), 357 (29), 339 (24), 309 (60), 308 (92), 290 (43), 230 (71), 200 (87), 199 (100), 181 (51), 139 (56), 135 (68), 105 (41), 77 (52)

HRMS (EI) Found: $M^{+\bullet}$, 492.0621. $C_{22}H_{25}IO_3Si$ requires $M^{+\bullet}$, 492.0618.

$[\alpha]_D$ +51.4 (*c* 0.5, $CHCl_3$)

Concentration of fraction B (R_f 0.4 in 99:1 v/v $CHCl_3$/MeOH) afforded *epoxide* ***108*** (104 mg, 10%) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.72 (4H, complex m, Ar-*H*), 7.49 – 7.38 (6H, complex m, Ar-*H*), 6.62 (1H, d, *J* 4.3 Hz, C5-*H*), 4.12 – 4.08 (2H, complex m, C2-*H* and C3-*H*), 3.46 (1H, ddd, *J* 4.3, 2.1 and 1.2 Hz, C1-*H*), 3.22 (1H, t, *J* 4.3 Hz, C6-*H*), 2.33 (1H, br s, -O*H*), 1.15 (9H, s, -CH_3)

^{13}C NMR (75 MHz, $CDCl_3$) δ 135.72 (2 x CH), 135.70 (2 x CH), 135.0 (CH), 133.0 (C), 132.8 (C), 130.1 (CH), 130.1 (CH), 127.90 (2 x CH), 127.87 (2 x CH), 105.3 (C), 78.4 (CH), 70.2 (CH), 56.6 (CH), 51.4 (CH), 26.8 (3 x CH_3), 19.3 (C)

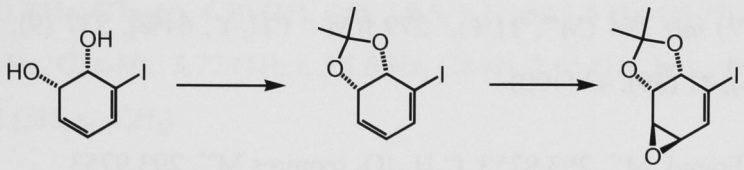
IR (thin film) ν_{max} 3467, 3071, 3049, 2931, 2857, 1960, 1891, 1824, 1697, 1616, 1589, 1471, 1427, 1362, 1253, 1115, 926, 821, 701 cm^{-1}

EIMS (70 eV) *m/z* 435 [$(M - C_4H_9\bullet)^+$, 5%], 357 (11), 308 (68), 230 (17), 199 (100), 181 (23), 135 (24), 105 (19), 77 (28), 57 (24)

HRMS (EI) Found: $(M - C_4H_9\bullet)^+$, 434.9909. $C_{22}H_{25}IO_3Si$ requires $(M - C_4H_9\bullet)^+$, 434.9913

$[\alpha]_D$ –67.8 (*c* 1.0, $CHCl_3$)

(3a*S*,5a*R*,6a*R*,6b*S*)-3a,5a,6a,6b-Tetrahydro-4-iodo-2,2-dimethyl-7-oxa-bicyclo[4.1.0]hepta-1(6),2-dieno[5,4-*d*][1,3]dioxole (109)



104 **112** **109**

A magnetically stirred solution of diol **104** (5.59 g, 23.4 mmol) in 2,2-dimethoxypropane (30 mL) maintained under a nitrogen atmosphere and protected from light was treated with *p*-toluenesulfonic acid (271 mg, 1.37 mmol). After 1.2 h at 18 °C, the reaction mixture was quenched with triethylamine (5 mL), diluted with DCM (50 mL) and washed with $NaHCO_3$ (1 x 50 mL of a saturated aqueous solution). The separated organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure at temperatures below 25 °C. The resulting pale-yellow oil, containing the unstable acetonide **112** (*ca.* 6.49 g, quantitative yield), was redissolved in DCM (200 mL) then cooled to 0 °C while being maintained under a nitrogen atmosphere and protected from light. The ensuing solution was treated with $NaHCO_3$ (8.83 g, 106 mmol) and *m*-chloroperbenzoic acid (15.73 g of a 77% pure solid, 91.1 mmol) then the resulting slurry was stirred for 23 h at 0 → 18 °C before being diluted with DCM (100 mL). The ensuing mixture was washed with $Na_2S_2O_3$ (2 x 200 mL of a 20% w/v aqueous solution), $NaHCO_3$ (1 x 300 mL of a saturated aqueous solution) and brine (1 x 300 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting white solid was subjected to flash chromatography (silica, 10:1 v/v hexane/EtOAc elution) and concentration of the appropriate fractions (R_f 0.3 in 20:1 v/v hexane/EtOAc) afforded the previously reported epoxide **109**[15] (5.30 g, 77%) as a white, crystalline solid.

MP 69 – 75 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (1H, dd, *J* 4.4 and 1.5), 4.85 (1H, ddd, *J* 6.6, 2.1, and 1.0 Hz), 4.37 (1H, dd, *J* 6.6 and 1.4 Hz), 3.61 (1H, dd, *J* 3.7 and 2.1 Hz), 3.19 (1H, m), 1.47 (3H, s), 1.43 (3H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1 (CH), 111.1 (C), 108.5 (C), 75.7 (CH), 72.0 (CH), 49.1 (CH), 48.5 (CH), 27.5 (CH_3), 26.2 (CH_3)

IR (thin film) ν_{max} 2987, 2932, 2879, 1617, 1368, 1229, 1074, 1041, 855, 748, 573 cm^{-1}

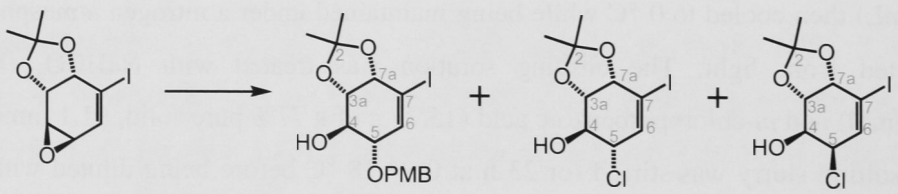
EIMS (70 eV) *m/z* 294 ($M^{+\bullet}$, 11%), 279 [$(M - CH_3\bullet)^+$, 64%], 237 (9), 207 (61), 110 (51), 109 (53), 81 (39), 43 (100)

HRMS (EI) Found: $M^{+\bullet}$, 293.9753. $C_9H_{11}IO_3$ requires $M^{+\bullet}$, 293.9753

$[\alpha]_D$ +126.7 (*c* 0.9, $CHCl_3$)

The spectroscopic data obtained on the material prepared as described above were in good agreement with those reported previously for compound **109**.[15]

(3a*S*,4*R*,5*S*,7a*S*)-5-(4-methoxybenzyloxy)-3a,4,5,7a-tetrahydro-7-iodo-2,2-dimethylbenzo[*d*][1,3]dioxol-4-ol (110) and (3a*S*,4*S*,5*S*,7a*S*)-5-Chloro-3a,4,5,7a-tetrahydro-7-iodo-2,2-dimethylbenzo[*d*][1,3]dioxol-4-ol (113) and (3a*S*,4*S*,5*R*,7a*S*)-5-chloro-3a,4,5,7a-tetrahydro-7-iodo-2,2-dimethylbenzo[*d*][1,3]dioxol-4-ol (114)



109 **110** **113** **114**

Method A

A magnetically stirred solution of epoxide **109** (121 mg, 0.41 mmol) and *p*-methoxybenzyl alcohol (111 mg, 0.80 mmol) in THF (1 mL), maintained at –78 °C under a nitrogen atmosphere, was treated with zinc(II) chloride (0.78 ml of a 1 M solution in Et_2O, 0.78 mmol). The ensuing mixture was stirred at 0 → 18 °C for 21 h,

then diluted with DCM (10 mL) and quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution). The separated aqueous phase washed with DCM (3 x 10 mL) and the combined organic phases dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting pale-yellow oil was subjected to flash chromatography (silica, 6:1 → 2:3 v/v hexane/EtOAc gradient elution) to furnish three fractions, A, B and C.

Concentration of fraction A (R_f 0.5 in 2:1 v/v hexane/EtOAc) afforded *dihalide* ***113*** (47 mg, 34%) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (1H, dd, *J* 2.1 and 0.6 Hz, C6-*H*), 4.70 (1H, ddd, *J* 6.3, 1.4, and 0.7 Hz, C7a-*H*), 4.30 (1H, ddd, *J* 8.5, 2.1, and 1.5 Hz, C5-*H*), 4.13 (1H, dd, *J* 8.7 and 6.3 Hz, C3a-*H*), 3.77 (1H, t, *J* 8.6 Hz, C4-*H*), 2.65 (1H, br s, -O*H*), 1.55 (3H, s, -CH_3), 1.42 (3H, s, -CH_3)

^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2 (C6), 110.5 (C2), 94.3 (C7), 79.4 (C7a), 77.2 (C3a), 73.8 (C4), 60.0 (C5), 28.0 (CH_3), 25.8 (CH_3)

IR (thin film) ν_{max} 3437, 2987, 2933, 1631, 1454, 1381, 1218, 1161, 1076, 866, 712 cm^{-1}

EIMS (70 eV) *m/z* 330 ($M^{+\bullet}$, <1%), 317 and 315 [$(M - CH_3\bullet)^+$, 48 and 96%], 257 (8), 255 (19), 209 (6), 207 (10), 191 (6), 130 (11), 128 (29), 121 (9), 110 (38), 101 (13), 81 (27), 59 (27), 43 (100)

HRMS (EI) Found: $(M - CH_3\bullet)^+$, 314.9283. $C_9H_{12}{}^{35}ClIO_3$ requires $(M - CH_3\bullet)^+$, 314.9285

$[\alpha]_D$ −14.3 (*c* 0.8, $CHCl_3$)

Concentration of fraction B (R_f 0.6 in 2:1 hexane/EtOAc) afforded *dihalide* ***114*** (41 mg, 30%) as a white, crystalline solid.

MP 102 – 105 °C

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.46 (1H, d, *J* 3.5, C6-*H*), 4.68 (1H, d, *J* 5.6 Hz, C7a-*H*), 4.66 (1H, td, *J* 3.5 and 1.1 Hz, C5-*H*), 4.42 (1H, t, *J* 5.6 Hz, C3a-*H*), 4.20 (1H, dd, *J* 5.7 and 3.5 Hz, C6-*H*), 2.31 (1H, br s, -O*H*), 1.45 (3H, s, -CH_3), 1.41 (3H, s, -CH_3)

^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3 (C6), 110.0 (C2), 101.2 (C7), 78.1 (C7a), 75.9 (C3a), 69.0 (C4), 58.5 (C5), 27.6 (CH_3), 26.1 (CH_3)

IR (thin film) ν_{max} 3390, 2985, 2949, 2875, 1624, 1457, 1380, 1221, 1161, 1108, 975, 911, 886, 869, 835, 797, 596 cm^{-1}

EIMS (70 eV) *m/z* 332 and 330 ($M^{+\bullet}$, 2% and 5%), 317 and 315 [$(M - CH_3\bullet)^+$, 48% and 100%], 274 (4), 272 (12), 255 (7), 209 (7), 207 (9), 191 (6), 130 (21), 128 (38), 110 (46), 101 (18), 81 (21), 59 (29), 43 (93)

HRMS (EI) Found: $M^{+\bullet}$, 329.9514. $C_9H_{12}{}^{35}ClIO_3$ requires $M^{+\bullet}$, 329.9520

$[\alpha]_D$ –17.3 (*c* 0.9, $CHCl_3$)

Concentration of fraction C (R_f 0.3 in 2:1 v/v hexane/EtOAc) afforded the desired *compound* ***110*** (46 mg, 26%) as a white, crystalline solid.

MP 99 – 100 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (2H, m, Ar-*H*), 6.89 (2H, m, Ar-*H*), 6.53 (1H, m, C6-*H*), 4.67 (1H, d, *J* 7.0 Hz, C7a-*H*), 4.66 (1H, d, *J* 11.3 Hz, CH_2), 4.54 (1H, d, *J* 11.3 Hz, CH_2), 4.12 (1H, dd, *J* 8.9 and 6.6 Hz, C3a-*H*), 3.83 (1H, m, C5-*H*), 3.81 (3H, s, -OCH_3), 3.67 (1H, t, *J* 8.8 Hz, C4-*H*), 2.66 (1H, br s, -O*H*), 1.53 (3H, s, -CH_3), 1.40 (3H, s, -CH_3)

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4 (C), 141.0 (CH), 129.6 (2 x CH), 129.3 (C), 113.9 (2 x CH), 110.2 (C), 92.9 (C), 79.4 (CH), 79.0 (CH), 77.1 (CH), 72.6 (CH), 71.8 (CH_2), 55.3 (CH_3), 28.0 (CH_3), 25.7 (CH_3)

IR (thin film) ν_{max} 3464, 2990, 2935, 2866, 1611, 1514, 1459, 1375, 1249, 1165, 1069, 870, 820 cm^{-1}

EIMS (70 eV) *m/z* 432 ($M^{+\bullet}$, 3%), 238 (20), 137 (35), 121 (100), 109 (20)

HRMS (EI) Found: $M^{+\bullet}$, 432.0431. $C_{17}H_{21}IO_5$ requires $M^{+\bullet}$, 432.0434

$[\alpha]_D$ +44.5 (*c* 0.9, $CHCl_3$)

Method B

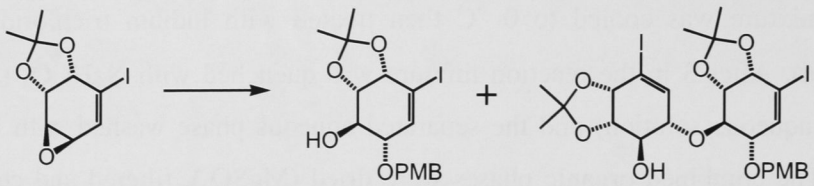
A magnetically stirred solution of *p*-methoxybenzyl alcohol (237 mg, 1.68 mmol) in DCM (2 mL) maintained under a nitrogen atmosphere was treated with activated, powdered, 4 Å molecular sieves (*ca.* 100 mg). The resulting slurry was stirred at 18 °C for 1 h then treated with epoxide **109** (100 mg, 0.34 mmol) and DCM (0.2 mL). The ensuing mixture was cooled to 0 °C then treated with indium trichloride (41 mg, 0.19 mmol). After 3 h, the reaction mixture was quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) and the separated aqueous phase washed with DCM (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the resulting pale-yellow oil subjected to flash chromatography (silica, 10:1 → 1:1 v/v hexane/EtOAc gradient elution) to afford three fractions, A, B and C.

Concentration of fraction A (R_f 0.5 in 2:1 v/v hexane/EtOAc) afforded *dihalide* ***113*** (15 mg, 14%) as a pale-yellow oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **113** prepared by Method A.

Concentration of fraction B (R_f 0.6 in 2:1 hexane/EtOAc) afforded *dihalide* ***114*** (33 mg, 29%) as a white, crystalline solid. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **114** prepared by Method A.

Concentration of fraction C (R_f 0.3 in 2:1 v/v hexane/EtOAc) afforded *compound* ***110*** (80 mg, 54%) as a white, crystalline solid. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **110** prepared by Method A.

(3a*S*,4*R*,5*S*,7a*S*)-5-(4-Methoxybenzyloxy)-3a,4,5,7a-tetrahydro-7-iodo-2,2-dimethylbenzo[*d*][1,3]dioxol-4-ol (110) and (3a*S*,4*R*,5*S*,7a*S*)-5-((3a*S*,4*R*,5*S*,7a*S*)-5-(4-methoxybenzyloxy)-3a,4,5,7a-tetrahydro-7-iodo-2,2-dimethylbenzo[*d*][1,3]dioxol-4-yloxy)-3a,4,5,7a-tetrahydro-7-iodo-2,2-dimethylbenzo[*d*][1,3]dioxol-4-ol (115)



109 **110** **115**

A magnetically stirred solution of *p*-methoxybenzyl alcohol (454 mg, 3.29 mmol) in DCM (4 mL) maintained under a nitrogen atmosphere was treated with activated, powdered, 4 Å molecular sieves (*ca.* 0.5 g). The resulting slurry was stirred at 18 °C for 4 h then treated with epoxide **109** (384 mg, 1.31 mmol) and DCM (4 mL). The ensuing mixture was cooled to 0 °C then treated with scandium(III) triflate (69 mg, 0.140 mmol). After 1.3 h, the reaction mixture was quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) and the separated aqueous phase washed with DCM (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the resulting off-white solid subjected to flash chromatography (silica, 20:1 → 2:1 v/v hexane/EtOAc gradient elution). Concentration of the appropriate fractions (R_f 0.3 in 2:1 v/v hexane/EtOAc) afforded compounds **110** and **115** (455 mg of a 5:1 mixture) as a white amorphous solid. This material was dissolved in hot EtOAc (2 mL) then hot hexane (6 mL) was added before the ensuing mixture was slowly cooled to 4 °C and then stored at this temperature for 16 h. Filtration of the resulting crystals furnished *binary complex **115*** (113 mg, 24%) as a white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (2H, m), 6.94 (2H, m), 6.58 (1H, m), 6.50 (1H, m), 4.72 (1H, d, *J* 6.9 Hz), 4.64 (1H, d, *J* 10.6 Hz), 4.62 (1H, d, *J* 6.3 Hz), 4.48 (1H, d, *J* 11.1 Hz), 3.89 (1H, dt, *J* 8.7 and 1.4 Hz), 3.84 (1H, m), 3.83 (3H, s), 3.61 (1H, br t, *J* 8.5 Hz), 3.50 (1H, t, *J* 8.9 Hz), 1.55 (3H, s), 1.54 (3H, s), 1.40 (3H, s), 1.38 (3H, s) (signal due to the hydroxyl proton was not observed)

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6 (C), 143.0 (CH), 140.6 (CH), 130.2 (2 x CH), 128.6 (C), 114.2 (2 x CH), 110.7 (C), 110.2 (C), 92.2 (C), 92.1 (C), 85.0 (CH), 83.8 (CH), 79.8 (CH), 79.3 (CH, two coincident signals), 77.2 (CH), 76.7 (CH), 73.9 (CH), 71.9 (CH_2), 55.3 (CH_3), 28.0 (CH_3), 27.6 (CH_3), 25.6 (CH_3), 25.4 (CH_3)

IR (thin film) ν_{max} 3471, 2983, 2929, 2876, 1612, 1514, 1376, 1358, 1249, 1214, 1163, 1090, 1070, 1038, 997, 868, 790, 746 cm^{-1}

ESI-MS (positive ion mode) *m/z* 749 [$(M + Na)^+$, 18%], 121 (100)

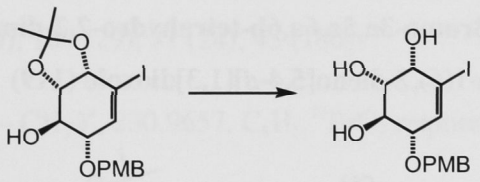
HRMS (ESI, positive ion mode) Found: $(M + Na)^+$, 749.0055. $C_{26}H_{32}I_2O_8$ requires $(M + Na)^+$, 749.0084

$[\alpha]_D$ +54.3 (*c* 0.3, $CHCl_3$)

Concentration of the filtrate derived from the fractional crystallisation of compound **115** as detailed above afforded *alcohol **110*** (338 mg, 60%) as a white, crystalline solid.

The spectral data derived from this material were in good agreement with those obtained from the sample of compound **110** prepared as described on page 114.

(1*S*,2*S*,3*S*,6*S*)-6-(4-Methoxybenzyloxy)-4-iodocyclohex-4-ene-1,2,3-triol (116)



110 **116**

A magnetically stirred solution of acetonide **110** (315 mg, 0.73 mmol) in THF (10 mL) was treated with trichloroacetic acid (2.02 g, 12.4 mmol) and water (2 mL). The resulting slurry was stirred for 9 d at 18 °C before being quenched with $NaHCO_3$ (50 mL of a saturated aqueous solution) and extracted with Et_2O (8 x 50 mL). The combined organic fractions were dried, filtered and concentrated under reduced pressure. The resulting white solid was dissolved in hot EtOAc (3 mL) and then hot hexane (4 mL) was added before the ensuing mixture was slowly cooled to 4 °C and

then stored at this temperature for 24 h. Filtration of the resulting crystals furnished *triol* ***116*** (177 mg, 63%) as a white, crystalline solid.

MP 139 – 141 °C

^{1}H NMR (300 MHz, CD_3OD) δ 7.29 (2H, m), 6.89 (2H, m), 6.36 (1H, d, *J* 2.2 Hz), 4.62 (2H, s), 4.22 (1H, d, *J* 4.1 Hz), 3.81 – 3.79 (1H, complex m), 3.78 (3H, s), 3.75 (1H, t, *J* 7.6 Hz), 3.51 (1H, dd, *J* 9.8 and 4.1 Hz) (signals due to the three hydroxyl protons were not observed)

^{13}C NMR (75 MHz, CD_3OD) δ 160.8 (C), 141.1 (CH), 131.6 (C), 130.7 (2 x CH), 114.7 (2 x CH), 100.4 (C), 82.7 (CH), 77.7 (CH), 72.8 (CH_2), 72.3 (CH), 71.6 (CH), 55.6 (CH_3)

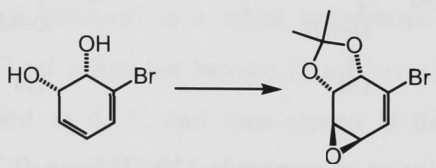
IR (KBr disk) ν_{max} 3444, 3369, 2966, 2906, 2892, 2839, 1633, 1613, 1513, 1456, 1296, 1241, 1136, 1080, 1026, 973, 817, 692 cm^{-1}

EIMS (70 eV) *m/z* 392 ($M^{+\bullet}$, 23%), 238 (26), 137 (92), 121 (100), 109 (42), 77 (31)

HRMS (EI) Found: $M^{+\bullet}$, 392.0126. $C_{14}H_{17}IO_5$ requires $M^{+\bullet}$, 392.0121

$[\alpha]_D$ +8.7 (*c* 1.0, MeOH)

(3a*S*,5a*R*,6a*R*,6b*S*)-4-Bromo-3a,5a,6a,6b-tetrahydro-2,2-dimethyl-7-oxabicyclo[4.1.0]hepta-1(6),2-dieno[5,4-*d*][1,3]dioxole (119)



3 **119**

A magnetically stirred solution of diol **3** (8.01 g, 41.9 mmol) in 2,2-dimethoxypropane (30 mL) maintained under a nitrogen atmosphere was treated with *p*-toluenesulfonic acid (302 mg, 1.59 mmol). After 1.2 h at 18 °C, the reaction mixture was diluted with DCM (50 mL) and washed with $NaHCO_3$ (1 x 50 mL of a saturated aqueous solution). The separated organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure at temperatures below 25 °C. The resulting pale-yellow oil was then

redissolved in DCM (150 mL) and cooled to 0 °C while being maintained under a nitrogen atmosphere and the ensuing solution was treated with *m*-chloroperbenzoic acid (14.6 g of a 77% pure solid, 84.5 mmol). The resulting slurry was stirred at 0 → 18 °C for 18 h before being diluted with DCM (100 mL) then washed with $Na_2S_2O_3$ (2 x 100 mL of a 20% w/v aqueous solution), $NaHCO_3$ (1 x 150 mL of a saturated aqueous solution) and brine (1 x 150 mL). The separated organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the previously reported epoxide **119**[16] (10.35 g, quantitative yield) as an off-white, crystalline solid. This material was used, without further purification, in the next step of the reaction sequence.

MP 75 – 77 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (1H, dd, *J* 4.5 and 1.2 Hz), 4.84 (1H, ddd, *J* 6.7, 1.8 and 1.1 Hz), 4.38 (1H, dd, *J* 6.7 and 1.0 Hz), 3.56 (1H, dd, *J* 3.7 and 1.9 Hz), 3.31 (1H, m), 1.43 (3H, s), 1.40 (3H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 129.7 (C), 126.4 (CH), 111.3 (C), 73.9 (CH), 72.5 (CH), 49.3 (CH), 48.1 (CH), 27.4 (CH_3), 25.9 (CH_3)

IR (thin film) ν_{max} 2991, 2891, 1627, 1368, 1213, 1054, 1041, 861 cm^{-1}

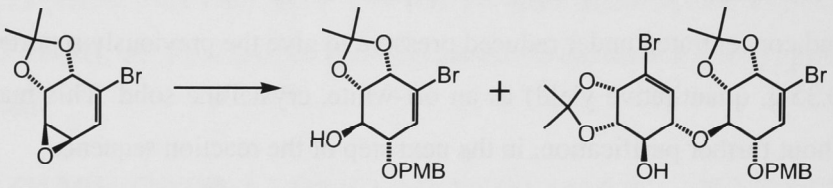
EIMS (70 eV) *m/z* 248 and 246 ($M^{+\bullet}$, <1%), 233 and 231 [$(M - CH_3\bullet)^+$, 18%], 191 and 189 (6), 161 and 159 (20), 109 (29), 81 (24), 43 (100)

HRMS (EI) Found: $(M - CH_3\bullet)^+$, 230.9657. $C_9H_{11}{}^{79}BrO_3$ requires $(M - CH_3\bullet)^+$, 230.9657

$[\alpha]_D$ +141.7 (*c* 1.0, $CHCl_3$)

The spectroscopic data obtained on the material prepared as described above were in good agreement with those reported previously for compound **119**.[16]

(3a*S*,4*R*,5*S*,7a*S*)-5-(4-Methoxybenzyloxy)-7-bromo-3a,4,5,7a-tetrahydro-2,2-dimethylbenzo[*d*][1,3]dioxol-4-ol (120) and (3a*S*,4*R*,5*S*,7a*S*)-5-((3a*S*,4*R*,5*S*,7a*S*)-5-(4-methoxybenzyloxy)-7-bromo-3a,4,5,7a-tetrahydro-2,2-dimethylbenzo[*d*][1,3]dioxol-4-yloxy)-7-bromo-3a,4,5,7a-tetrahydro-2,2-dimethylbenzo[*d*][1,3]dioxol-4-ol (121)



119 **120** **121**

A magnetically stirred solution of *p*-methoxybenzyl alcohol (997 mg, 7.22 mmol) and activated, powdered 4 Å molecular sieves (*ca.* 1 g) in DCM (100 mL) maintained under a nitrogen atmosphere was stirred at 18 °C for 2 h before being cooled to 0 °C and treated with scandium(III) triflate (64 mg, 0.131 mmol). A solution of epoxide **119** (960 mg, 3.88 mmol) in DCM (12 mL) was prepared and added dropwise to the reaction mixture over 0.5 h, and the resulting mixture stirred for 2.5 h before being quenched with $NaHCO_3$ (100 mL of a saturated aqueous solution). The separated aqueous phase was extracted with DCM (1 x 50 mL) and the combined organic phases dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting off-white solid was subjected to flash chromatography (10:1 → 2:1 v/v hexane/EtOAc gradient elution) and concentration of the appropriate fractions (R_f 0.3 in 2:1 v/v hexane/EtOAc) afforded compounds **120** and **121** (810 mg of a 7:2 mixture). The white solid thus obtained was dissolved in hot EtOAc (10 mL) and hot hexane (30 mL) was added before the ensuing mixture was slowly cooled to 4 °C and then stored at this temperature for 16 h. Filtration of the resulting crystals furnished *binary complex **121*** (158 mg, 26%) as a white, crystalline solid.

MP decomposition above 172 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (2H, m), 6.93 (2H, m), 6.32 (1H, d, *J* 1.5 Hz), 6.22 (1H, d, *J* 1.7 Hz), 4.72 (1H, d, *J* 6.3 Hz), 4.65 (1H, d, *J* 10.7 Hz), 4.62 (1H, d, *J* 6.3 Hz), 4.46 (1H, d, *J* 10.7 Hz), 4.24 (1H, dd, *J* 9.2 and 6.7 Hz), 4.12 (1H, dd, *J* 9.3 and 6.7 Hz), 3.92 (1H, br d, *J* 8.7 Hz), 3.85 (1H, br d, *J* 8.5 Hz), 3.82 (3H, s), 3.64 (1H, t, *J* 8.8 Hz),

3.53 (1H, t, *J* 8.9 Hz), 1.57 (3H, s), 1.56 (3H, s), 1.41 (3H, s), 1.39 (3H, s) (signal due to the hydroxyl proton was not observed)

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6 (C), 135.0 (CH), 132.5 (CH), 130.1 (2 x CH), 128.5 (C), 118.0 (C), 117.6 (C), 114.1 (2 x CH), 111.3 (C), 110.8 (C), 84.1 (CH), 84.0 (CH), 78.2 (CH), 77.3 (CH), 76.9 (CH, three coincident signals), 73.8 (CH), 71.8 (CH_2), 55.2 (CH_3), 28.0 (CH_3), 27.5 (CH_3), 25.7 (CH_3), 25.5 (CH_3)

IR (KBr disk) ν_{max} 3470, 2979, 2935, 2906, 2871, 2831, 1735, 1643, 1615, 1514, 1369, 1247, 1215, 1170, 1073, 911, 870, 799 cm^{-1}

ESI-MS (positive ion mode) *m/z* 657 and 655 and 653 [$(M + Na)^+$, 52 and 100 and 50%]

HRMS (ESI, positive ion mode) Found: $(M + Na)^+$, 653.0348. $C_{26}H_{32}{}^{79}Br_2O_8$ requires $(M + Na)^+$, 653.0362

$[\alpha]_D$ +47.5 (*c* 1.0, $CHCl_3$)

Concentration of the filtrate derived from the fractional crystallisation of compound **121** as detailed above afforded *compound **120*** (643 mg, 43%) as a cloudy, white oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (2H, m), 6.87 (2H, m), 6.23 (1H, d, *J* 1.8 Hz), 4.63 (1H, d, *J* 11.1 Hz), 4.62 (1H, d, *J* 7.6 Hz), 4.54 (1H, d, *J* 11.1 Hz), 4.12 (1H, dd, *J* 8.8 and 6.6 Hz), 3.83 (1H, dt, *J* 8.8 and 6.5 Hz), 3.77 (3H, s), 3.68 (1H, t, *J* 8.8 Hz), 3.02 (1H, b s, -O*H*), 1.51 (3H, s), 1.38 (3H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3 (C), 132.9 (CH), 129.5 (2 x CH), 118.4 (C), 114.0 (C), 113.9 (2 x CH), 110.8 (C), 77.9 (CH), 77.4 (CH), 77.0 (CH), 72.6 (CH), 71.8 (CH_2), 55.2 (CH_3), 28.0 (CH_3), 25.8 (CH_3)

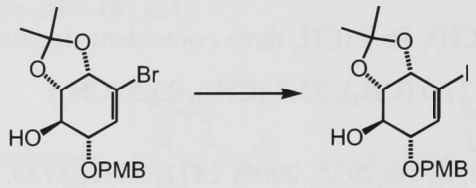
IR (thin film) ν_{max} 3459, 2990, 2935, 2837, 2285, 2059, 1886, 1644, 1612, 1514, 1463, 1381, 1245, 1173, 1066, 868, 822, 755 cm^{-1}

EIMS (70 eV) *m/z* 386 and 384 ($M^{+\bullet}$, 9%), 371 and 369 [$(M - CH_3\bullet)^+$, 3%], 247 (13), 192 and 190 (45), 137 (72), 121 (100), 101 (49), 83 (31)

HRMS (EI) Found: $M^{+\bullet}$, 384.0583. $C_{17}H_{21}{}^{79}BrO_5$ requires $M^{+\bullet}$, 384.0572

$[\alpha]_D$ +25.1 (*c* 1.1, $CHCl_3$)

(3a*S*,4*R*,5*S*,7a*S*)-5-(4-Methoxybenzyloxy)-3a,4,5,7a-tetrahydro-7-iodo-2,2-dimethylbenzo[*d*][1,3]dioxol-4-ol (110)

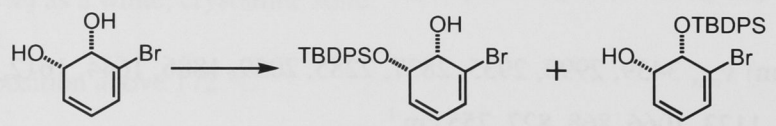


120 **110**

A magnetically stirred solution of acetonide **120** (80 mg, 0.21 mmol) in *n*-BuOH (0.75 mL) maintained under a nitrogen atmosphere was treated with cuprous iodide (3 mg, 16.3 μmol), sodium iodide (58 mg, 0.39 mmol) and *N*,-*N*'-dimethylethylenediamine (3 μL, 28.2 μmol). The reaction vessel was then sealed and heated to 120 °C for 26 h. The resulting mixture was cooled then diluted with DCM (10 mL) and washed with $NaHCO_3$ (1 x 10 mL of a saturated aqueous solution) then brine (1 x 10 mL). The separated organic phase was dried ($MgSO_4$), filtered then concentrated under reduced pressure and the resulting brown oil was subjected to flash chromatography (10:1 → 2:1 v/v hexane/EtOAc gradient elution). Concentration of the appropriate fractions (R_f 0.3 in 2:1 v/v hexane/EtOAc) afforded *alkenyl iodide* ***110*** (74 mg, 83% yield) as a crystalline, white solid.

The spectral data derived from this material were in good agreement with those obtained from the sample of compound **110** prepared as described on page 114.

(1*S*,6*S*)-2-bromo-6-(*tert*-butyldiphenylsiloxy)cyclohexa-2,4-dienol (122) and (1*S*,6*S*)-5-Bromo-6-(*tert*-butyldiphenylsiloxy)cyclohexa-2,4-dienol (123)



3 **122** **123**

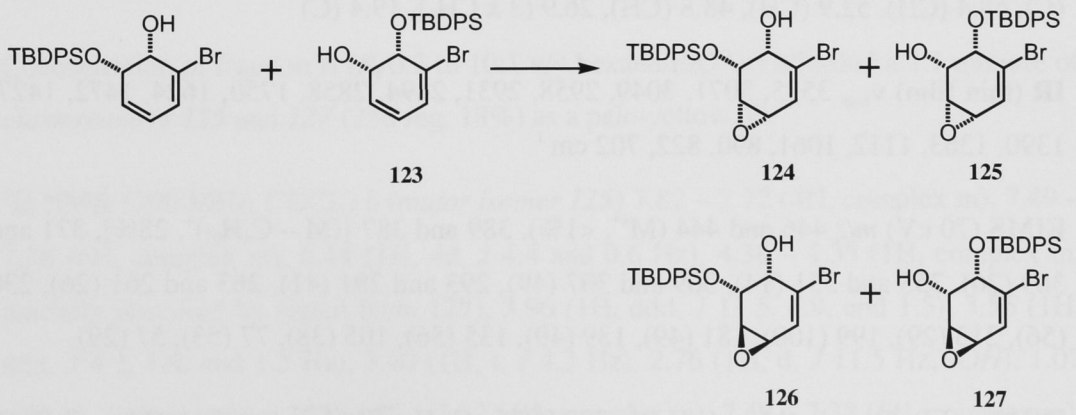
A magnetically stirred solution of diol **3** (595 mg, 3.12 mmol) in DCM (5 mL) maintained at 18 °C under a nitrogen atmosphere was treated with imidazole (635 mg, 9.33 mmol) and *t*-butyldiphenylchlorosilane (948 mg, 3.45 mmol). After 2 h the

reaction mixture was diluted with Et_2O (30 mL) and washed with water (2 x 30 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure at temperatures below 25 °C. The resulting pale-yellow oil (1.34 g of a 4:1 mixture of *compounds* ***122*** and ***123***, quantitative yield) was immediately used, as obtained, in the next step of the reaction sequence.

^{1}H NMR (300 MHz, $CDCl_3$) δ (*major isomer* ***122***) 7.76 – 7.69 (4H, complex m), 7.51 – 7.39 (6H, complex m), 6.32 (1H, m), 5.69 – 5.67 (2H, complex m), 4.60 (1H, m), 4.08 (1H, d, *J* 6.3 Hz), 2.94 (1H, br s, -O*H*), 1.12 (9H, s); (*minor isomer* ***123***) 7.76 – 7.69 (4H, complex m), 7.51 – 7.39 (6H, complex m), 6.35 (1H, m), 5.87 – 5.84 (2H, complex m), 4.28 (1H, d, *J* 5.6 Hz), 4.16 (1H, m), 3.02 (1H, br s, -O*H*), 1.12 (9H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ (*major isomer* ***122***) 135.7 (2 x CH), 135.6 (2 x CH), 132.9 (C), 132.7 (C), 130.2 (CH), 130.0 (CH), 129.1 (CH), 127.82 (2 x CH), 127.75 (2 x CH), 126.9 (CH), 125.4 (C), 123.4 (CH), 72.5 (CH), 71.4 (CH), 26.9 (3 x CH_3), 19.3 (C)

(1*S*,2*R*,3*S*,6*S*)-4-Bromo-2-(*tert*-butyldiphenylsiloxy)-7-oxabicyclo[4.1.0]hept-4-en-3-ol (124) and (1*R*,2*S*,3*S*,6*S*)-4-bromo-3-(*tert*-butyldiphenylsiloxy)-7-oxabicyclo[4.1.0]hept-4-en-2-ol (125) and (1*R*,2*R*,3*S*,6*R*)-4-bromo-2-(*tert*-butyldiphenylsiloxy)-7-oxabicyclo[4.1.0]hept-4-en-3-ol (126) and (1*S*,2*S*,3*S*,6*R*)-4-bromo-3-(*tert*-butyldiphenylsiloxy)-7-oxabicyclo[4.1.0]hept-4-en-2-ol (127)



A magnetically stirred solution compounds **122** and **123** (1.34 g of a 4:1 mixture, 3.12 mmol, obtained as described on the previous page) in DCM (50 mL) maintained at 0 °C under a nitrogen atmosphere was treated with *m*-chloroperbenzoic acid (1.70 g of a

77% pure solid, 7.60 mmol). The resulting slurry was stirred at 0 → 18 °C for 16 h before being diluted with Et_2O (100 mL) then washed with $Na_2S_2O_5$ (2 x 100 mL of a 20% w/v aqueous solution), $NaHCO_3$ (1 x 100 mL of a saturated aqueous solution) and brine (1 x 100 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 10:1 → 5:1 v/v hexane/EtOAc gradient elution) to give two fractions, A and B.

Concentration of fraction A (R_f 0.5 in 10:1 v/v hexane/EtOAc) afforded diastereomers **124** and **126** (1.12 g of a 5:2 mixture, 81%) as a pale-yellow oil that was subjected to further flash chromatography (silica, $CHCl_3$ elution) to give two fractions, A1 and A2.

Concentration of fraction A1 (R_f 0.4 in $CHCl_3$) afforded *compound **124*** (315 mg, 23%) as a white, crystalline solid.

MP 142 – 145 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.67 (4H, complex m), 7.49 – 7.38 (6H, complex m), 6.50 (1H, dd, *J* 4.6 and 2.3 Hz), 4.60 (1H, m), 4.06 (1H, ddd, *J* 10.7, 4.8 and 2.3 Hz), 3.17 – 3.16 (2H, complex m), 2.58 (1H, d, *J* 10.7 Hz, -O*H*), 1.08 (9H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8 (2 x CH), 135.6 (2 x CH), 132.8 (C), 132.3 (C), 130.3 (CH), 130.2 (CH), 129.6 (C) 128.1 (2 x CH), 127.9 (2 x CH), 125.4 (CH), 69.4 (C), 68.4 (CH), 52.9 (CH), 48.8 (CH), 26.9 (3 x CH_3), 19.4 (C)

IR (thin film) ν_{max} 3555, 3071, 3049, 2958, 2931, 2894, 2858, 1750, 1624, 1472, 1427, 1390, 1363, 1112, 1061, 890, 822, 702 cm^{-1}

EIMS (70 eV) *m/z* 446 and 444 ($M^{+\bullet}$, <1%), 389 and 387 [$(M - C_4H_9\bullet)^+$, 28%], 371 and 369 (26), 353 and 351 (14), 309 and 307 (49), 293 and 291 (41), 263 and 261 (26), 230 (56), 213 (29), 199 (100), 181 (49), 139 (49), 135 (56), 105 (38), 77 (53), 57 (29)

HRMS (EI) Found: $(M - C_4H_9\bullet)^+$, 387.0056. $C_{22}H_{25}{}^{79}BrO_3Si$ requires $(M - C_4H_9\bullet)^+$, 387.0052

$[\alpha]_D$ +60.7 (*c* 0.9, $CHCl_3$)

Concentration of fraction A2 (R_f 0.3 in $CHCl_3$) afforded *compound* ***126*** (801 mg, 58%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.72 (4H, complex m), 7.50 – 7.39 (6H, complex m), 6.34 (1H, dd, *J* 4.4 and 0.7 Hz), 4.09 (1H, dd, *J* 4.9 and 1.0 Hz), 4.01 (1H, dddd, *J* 10.2, 4.8, 2.2, and 0.7 Hz), 3.44 (1H, ddd, *J* 4.3, 2.3, and 1.0 Hz), 3.33 (1H, t, *J* 4.4 Hz), 2.81 (1H, d, *J* 10.2 Hz, -O*H*), 1.14 (9H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7 [4 x CH (2 x two coincident signals)], 133.0 (C), 132.7 (C), 130.5 (C), 130.13 (CH), 130.08 (CH), 127.9 [4 x CH (2 x two coincident signals)], 126.9 (CH), 75.2 (CH), 70.5 (CH), 56.7 (CH), 50.3 (CH), 26.8 (3 x CH_3), 19.3 (C)

IR (thin film) ν_{max} 3529, 3071, 3049, 2957, 2932, 2858, 1630, 1472, 1427, 1114, 1054, 929, 822, 703 cm^{-1}

EIMS (70 eV) *m/z* 389 and 387 [$(M - C_4H_9\bullet)^+$, 5%], 371 and 369 (7), 309 and 307 (46), 283 and 281 (26), 263 and 261 (24), 231 and 229 (16), 213 (18), 199 (100), 181 (33), 135 (36), 105 (26), 77 (34)

HRMS (EI) Found: $(M - C_4H_9\bullet)^+$, 387.0054. $C_{22}H_{25}{}^{79}BrO_3Si$ requires $(M - C_4H_9\bullet)^+$, 387.0052

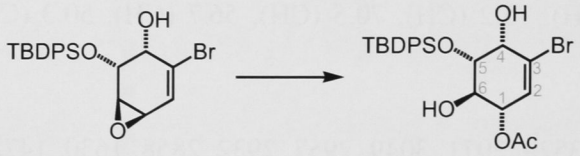
$[\alpha]_D$ –116.1 (*c* 1.0, $CHCl_3$)

Concentration of fraction B (R_f 0.3 in 10:1 v/v hexane/EtOAc) afforded a 2:1 mixture of *diastereomers* ***125*** and ***127*** (250 mg, 18%) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ (*major isomer* ***125***) 7.82 – 7.72 (4H, complex m), 7.49 – 7.38 (6H, complex m), 6.44 (1H, dd, *J* 4.4 and 0.6 Hz), 4.38 – 4.35 (1H, complex m, partially obscured by signal from **127**), 3.96 (1H, ddd, *J* 11.5, 4.9, and 1.5), 3.56 (1H, ddd, *J* 4.2, 1.9, and 1.5 Hz), 3.40 (1H, t, *J* 4.3 Hz), 2.76 (1H, d, *J* 11.5 Hz, -O*H*), 1.07 (9H, s); (*minor isomer* ***127***) 7.82 – 7.72 (4H, complex m), 7.49 – 7.38 (6H, complex m), 6.46 (1H, dd, *J* 4.4 and 2.3 Hz), 4.38 – 4.35 (1H, complex m, partially obscured by signal from **125**), 4.01 (1H, ddd, *J* 4.8, 2.9, and 0.8 Hz), 3.43 (1H, dd, *J* 3.8 and 2.8 Hz), 3.27 (1H, m), 2.44 (1H, br s, -O*H*), 1.17 (9H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ (*major isomer **125***) 136.3 (2 x CH), 135.8 (2 x CH), 132.8 (C), 132.2 (C), 130.0 (CH), 129.8 (CH), 129.3 (C), 128.0 (2 x CH), 127.4 (2 x CH), 125.9 (CH), 74.9 (CH), 70.0 (CH), 55.4 (CH), 49.1 (CH), 27.0 (3 x CH_3), 19.6 (C); (*minor isomer **127***) 136.2 (2 x CH), 135.7 (2 x CH), 133.1 (C), 131.8 (C), 130.7 (C), 130.3 (CH), 130.2 (CH), 128.0 (2 x CH), 127.8 (2 x CH), 125.9 (CH), 69.6 (CH), 66.5 (CH), 52.6 (CH), 48.3 (CH), 27.1 (3 x CH_3), 19.6 (C)

(1*S*,4*S*,5*S*,6*R*)-3-Bromo-5-(*tert*-butyldiphenylsiloxy)-4,6-dihydroxycyclohex-2-enyl acetate (128)



126 **128**

A magnetically solution of sodium acetate (302 mg, 3.68 mmol) in acetic acid (8 mL) maintained under a nitrogen atmosphere was treated with epoxide **126** (259 mg, 0.58 mmol). The resulting solution was stirred at 18 °C for 7 h before being quenched by the slow addition of $NaHCO_3$ (50 mL of a saturated aqueous solution). The ensuing mixture was extracted with DCM (5 x 50 mL) and the combined organic phases washed with water (1 x 200 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting colourless oil was subjected to flash chromatography (silica, 4:1 v/v hexane/EtOAc + 1% MeOH elution) and concentration of the appropriate fractions (R_f 0.3 in 2:1 v/v hexane/EtOAc + 1% MeOH) furnished *1,3-diol **128*** (179 mg, 61%) as a white, amorphous solid.

MP 43 – 47 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (2H, m, Ar-*H*), 7.67 (2H, m, Ar-*H*), 7.50 – 7.38 (6H, complex m, Ar-*H*), 6.19 (1H, d, *J* 4.7 Hz, C2-*H*), 5.26 (1H, t, *J* 4.0 Hz, C1-*H*), 4.20 (1H, br d, *J* 4.0 Hz, C4-*H*), 4.07 (1H, dd, *J* 4.1 and 2.2 Hz, C5-*H*), 3.71 (1H, br s, C6-*H*), 2.97 – 2.93 (2H, br s, two coincident -O*H* signals), 1.88 (3H, s, -C(O)CH_3), 1.13 (9H, s, -CH_3)

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (C), 135.8 (2 x CH), 135.6 (2 x CH), 132.7 (C), 132.5 (C), 130.21 (CH), 130.17 (CH), 128.5 (C), 128.0 (2 x CH), 127.9 (2 x CH), 126.8 (CH), 72.8 (CH), 71.8 (CH), 71.3 (CH), 70.8 (CH), 26.9 (3 x CH_3), 20.7 (CH_3), 19.4 (C)

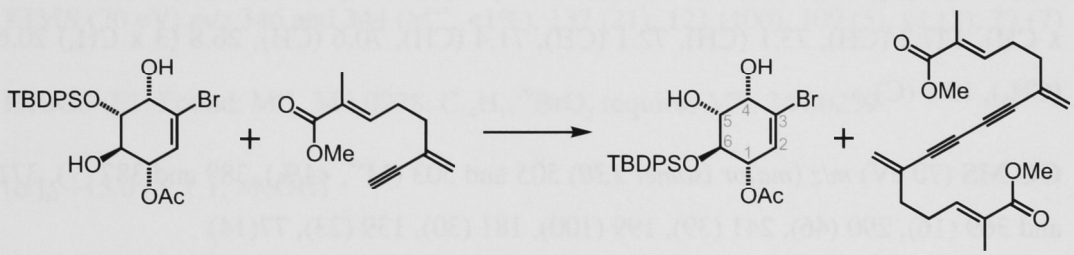
IR (KBr disk) ν_{max} 3454, 3072, 3052, 2933, 2859, 1965, 1738, 1642, 1472, 1428, 1373, 1232, 1113, 1078, 1022, 920, 856, 823, 738 cm^{-1}

ESI-MS (positive ion mode) *m/z* 529 and 527 [$(M + Na)^+$, 100%]

HRMS (ESI, positive ion mode) Found: $(M + Na)^+$, 529.0849. $C_{24}H_{29}{}^{81}BrO_5Si$ requires $(M + Na)^+$, 529.0845

$[\alpha]_D$ –106.9 (*c* 1.0, $CHCl_3$)

Dimethyl (2*E*,14*E*)-2,15-dimethyl-6,11-dimethylenehexadeca-2,14-dien-7,9-diynedioate (96) and (1*S*,4*S*,5*R*,6*S*)-3-Bromo-6-(*tert*-butyldiphenylsiloxy)-4,5-dihydroxycyclohex-2-enyl acetate (130)



128 **92** **130** **96**

A magnetically stirred solution of alkenyl bromide **128** (52 mg, 0.10 mmol) in THF (0.8 mL) maintained at 0 °C under a nitrogen atmosphere was treated, sequentially, with diisopropylamine (50 mg, 0.49 mmol), dichloro*bis*(triphenylphosphine)palladium (5 mg, 7.1 μmol), and cuprous iodide (3 mg, 16 μmol). The resulting mixture was treated, dropwise, with a solution of alkyne **92** (21 mg, 0.12 mmol) in THF (1 mL) and the ensuing green solution was stirred for an additional 16 h during which time the temperature was allowed to rise to 18 °C. The reaction mixture was then diluted with DCM (10 mL) and washed with water (1 x 10 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 4:1 v/v hexane/EtOAc + 1% MeOH elution) to afford two fractions, A and B.

Concentration of fraction A (R_f 0.6 in 2:1 v/v hexane/EtOAc + 1% MeOH) afforded *alkyne dimer* ***96*** (14 mg, 66%) as a clear, colourless oil. The spectral data derived from this material were in good agreement with those obtained from the sample of compound **96** prepared as described on page 109.

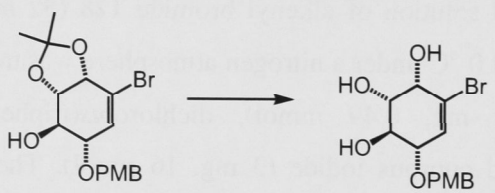
Concentration of fraction B (R_f 0.3 in 2:1 v/v hexane/EtOAc + 1% MeOH) afforded a 10:3 mixture of *compound* ***130*** and starting material **128** (51 mg, 100%) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ (*major isomer* ***130***) 7.72 (2H, m), 7.61 (2H, m), 7.48 – 7.39 (6H, complex m), 6.04 (1H, dd, *J* 3.6 and 1.0 Hz, C2-*H*), 5.26 (1H, m, C1-*H*), 4.08 – 4.02 (2H, complex m, C4-*H* and C5-*H*), 3.97 (1H, dd, *J* 5.8 and 2.1 Hz, C6-*H*), 3.07 (1H, d, *J* 9.6 Hz, C5-O*H*), 2.94 (1H, d, *J* 5.1 Hz, C4-O*H*), 1.74 (3H, s, -C(O)CH_3), 1.07 (9H, s, -CH_3)

^{13}C NMR (75 MHz, $CDCl_3$) δ (*major isomer* ***130***) 169.9 (C), 135.9 (2 x CH), 135.5 (2 x CH), 132.8 (C), 131.8 (C), 130.3 (CH), 130.1 (CH), 128.4 (C), 128.0 (2 x CH), 127.8 (2 x CH), 127.2 (CH), 73.1 (CH), 72.1 (CH), 71.4 (CH), 70.6 (CH), 26.8 (3 x CH_3) 20.6 (CH_3), 19.1 (C)

GC-MS (70 eV) *m/z* (*major isomer* ***130***) 505 and 503 ($M^{+\bullet}$, <1%), 389 and 387 (7), 371 and 369 (16), 290 (46), 241 (39), 199 (100), 181 (30), 139 (23), 77(14)

(1*S*,2*S*,3*S*,6*S*)-6-(4-Methoxybenzyloxy)-4-bromocyclohex-4-ene-1,2,3-triol (132)



120 **132**

A magnetically stirred solution of acetonide **120** (50 mg, 0.13 mmol) in THF (5 mL) was treated with trichloroacetic acid (115 mg, 0.71 mmol) and water (1 mL). The resulting slurry was stirred at 18 °C for 5 d before being quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution) and extracted with Et_2O (8 x 10 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under

reduced pressure. The resulting white solid was dissolved in hot EtOAc (1 mL) and then hot hexane (1.5 mL) was added before the ensuing mixture was slowly cooled to 4 °C and then stored at this temperature for 15 h. Filtration of the resulting crystals furnished *triol* ***132*** (32 mg, 71%) as a white, crystalline solid.

^{1}H NMR (300 MHz, CD_3OD) δ 7.31 (2H, m), 6.88 (2H, m), 6.11 (1H, d, *J* 2.2 Hz), 4.62 (2H, s), 4.19 (1H, d, *J* 4.3 Hz), 3.83 (1H, dd, *J* 7.6 and 2.2 Hz), 3.79 (1H, d, *J* 6.6 Hz), 3.77 (3H, s), 3.49 (1H, dd, *J* 10.0 and 4.3 Hz) (signals due to the three hydroxyl protons were not observed)

^{13}C NMR (75 MHz, CD_3OD) δ 160.8 (C), 132.7 (CH), 131.6 (C), 130.7 (2 x CH), 125.2 (C), 114.7 (2 x CH), 81.4 (CH), 74.7 (CH), 72.7 (CH_2), 72.4 (CH), 71.7 (CH), 55.6 (CH_3)

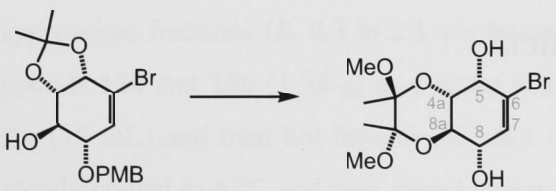
IR (thin film) ν_{max} 3369, 2934, 2836, 1642, 1612, 1514, 1463, 1303, 1250, 1175, 1075, 1033, 822, 699 cm^{-1}

EIMS (70 eV) *m/z* 346 and 344 ($M^{+\bullet}$, <1%), 137 (21), 121 (100), 109 (5), 91 (3), 77 (7)

HRMS (EI) Found: $M^{+\bullet}$, 344.0278. $C_{14}H_{17}{}^{79}BrO_5$ requires $M^{+\bullet}$, 344.0259

$[\alpha]_D$ +15.0 (*c* 1.1, MeOH)

(2*S*,3*S*,4a*R*,5*S*,8*S*,8a*R*)-6-Bromo-2,3,4a,5,8,8a-hexahydro-2,3-dimethoxy-2,3-dimethylbenzo[*b*][1,4]dioxine-5,8-diol (133)



120 **133**

A magnetically stirred solution of acetonide **120** (304 mg, 0.79 mmol) in MeOH (15 mL) maintained under a nitrogen atmosphere was treated with 2,3-butanedione (92 mg, 1.07 mmol), trimethylorthoformate (333 mg, 3.14 mmol) and camphorsulfonic acid (9 mg, 0.04 mmol). The reaction vessel was sealed and heated to 80 °C for 16 h. The resulting mixture was cooled then diluted with DCM (50 mL) and washed with

$NaHCO_3$ (1 x 50 mL of a saturated aqueous solution) then water (1 x 50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting white solid was subjected to flash chromatography (silica, 5:1 → 1:1 v/v hexane/EtOAc gradient elution) and concentration of the appropriate fractions (R_f 0.15 in 2:1 v/v hexane/EtOAc) furnished *1,4 diol* ***133*** (174 mg, 65%) as a white, crystalline solid.

MP 190 – 191 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (1H, d, *J* 2.3 Hz, C7-*H*), 4.33 (1H, d, *J* 4.1 Hz, C5-*H*), 4.23 (1H, dd, *J* 8.1 and 2.3 Hz, C8-*H*), 3.94 (1H, dd, *J* 11.0 and 8.1 Hz, C8a-*H*), 3.69 (1H, dd, *J* 11.0 and 4.1 Hz, C4a-*H*), 3.29 (3H, s, -OCH_3), 3.27 (3H, s, -OCH_3), 2.31 (2H, br s, two coincident -O*H*), 1.34 (3H, s, -CH_3), 1.33 (3H, s, -CH_3)

^{13}C NMR (75 MHz, $CDCl_3$) δ 134.0 (CH), 121.8 (C), 99.8 (C), 99.1 (C), 72.0 (CH), 70.7 (CH), 68.4 (CH), 67.4 (CH), 48.2 (CH_3), 48.0 (CH_3), 17.7 (CH_3), 17.6 (CH_3)

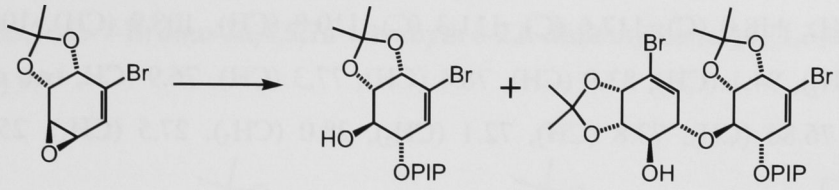
IR (KBr disk) ν_{max} 3432, 2992, 2950, 2836, 1639, 1456, 1377, 1137, 1077, 1032, 981, 917, 851 cm^{-1}

EIMS (70 eV) *m/z* 309 and 307 [(M – OCH_3•)$^+$, 10%], 191 and 189 (10), 174 and 172 (25), 111 (94), 101 (48), 83 (43), 75 (63), 69 (50), 55 (41), 43 (100)

HRMS (EI) Found: (M – CH_3O•)$^+$, 307.0181. $C_{12}H_{19}{}^{79}BrO_6$ requires (M – CH_3O•)$^+$, 307.0181

$[\alpha]_D$ +75.1 (*c* 1.0, $CHCl_3$)

(3a*S*,4*R*,5*S*,7a*S*)-5-((Benzo[*d*][1,3]dioxol-6-yl)methoxy)-7-bromo-3a,4,5,7a-tetrahydro-2,2-dimethylbenzo[*d*][1,3]dioxol-4-ol (134) and (3a*S*,4*R*,5*S*,7a*S*)-5-((3a*S*,4*R*,5*S*,7a*S*)-5-((benzo[*d*][1,3]dioxol-6-yl)methoxy)-7-bromo-3a,4,5,7a-tetrahydro-2,2-dimethylbenzo[*d*][1,3]dioxol-4-yloxy)-7-bromo-3a,4,5,7a-tetrahydro-2,2-dimethylbenzo[*d*][1,3]dioxol-4-ol (136)



119 **134** **136**

A magnetically stirred solution of piperonol (1.05 g, 6.89 mmol) in DCM (150 mL) maintained under a nitrogen atmosphere was treated with activated, powdered 4 Å molecular sieves (*ca.* 1 g). The resulting slurry was stirred at 18 °C for 1 h before being cooled to 0 °C and treated with scandium(III) triflate (120 mg, 0.24 mmol). A solution of epoxide **119** (1.03 g, 4.17 mmol) in DCM (10 mL) was prepared and added to the reaction mixture using a syringe pump at a rate of 4 mL/h. The reaction mixture was stirred for a further 0.75 h following complete addition of the epoxide solution, then quenched with $NaHCO_3$ (100 mL of a saturated aqueous solution). The separated aqueous phase was extracted with DCM (1 x 50 mL) and the combined organic phases were washed with brine (1 x 100 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting off-white solid was subjected to flash chromatography (silica, 10:1 → 5:1 v/v hexane/EtOAc gradient elution) and concentration of the appropriate fractions (R_f 0.3 in 2:1 v/v hexane/EtOAc) afforded a 10:3 mixture of compounds **134** and **136** (1.35 g) as a white solid. This material was dissolved in hot EtOAc (15 mL) and then hot hexane (30 mL) was added before the ensuing mixture was slowly cooled to 4 °C and then stored at this temperature for 16 h. Filtration of the resulting crystals furnished *binary complex* ***136*** (401 mg, 30%) as a white, crystalline solid.

MP 189 – 192 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 – 6.81 (3H, complex m), 6.29 (1H, d, *J* 1.5 Hz), 6.19 (1H, d, *J* 1.7), 5.98 (2H, s), 4.72 (1H, d, *J* 6.6 Hz), 4.62 (1H, d, *J* 6.6 Hz), 4.61

(1H, d, *J* 10.9 Hz), 4.43 (1H, d, *J* 10.9 Hz), 4.24 (1H, dd, *J* 9.2 and 6.7 Hz), 4.13 (1H, dd, *J* 9.2 and 6.7 Hz), 3.91 (1H, dt, *J* 8.5 and 1.4 Hz), 3.85 (1H, dt, *J* 8.5 and 1.5 Hz), 3.64 (1H, t, *J* 8.9 Hz), 3.53 (1H, t, *J* 8.9 Hz), 1.57 (3H, s), 1.55 (3H, s), 1.01 (3H, s), 1.39 (3H, s) (signal due to the hydroxyl proton was not observed)

^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8 (C), 147.6 (C), 134.8 (CH), 132.4 (CH), 130.2 (C), 122.2 (CH), 118.0 (C), 117.6 (C), 111.3 (C), 110.8 (CH), 108.9 (CH), 108.3 (CH), 101.1 (CH_2), 84.1 (CH), 83.9 (CH), 78.4 (CH), 77.3 (CH), 76.9 (CH, two coincident signals), 76.86 (CH), 73.8 (CH), 72.1 (CH_2), 28.0 (CH_3), 27.5 (CH_3), 25.7 (CH_3), 25.5 (CH_3)

IR (thin film) ν_{max} 3471, 2985, 2888, 1639, 1492, 1444, 1382, 1242, 1216, 1074, 1039, 996, 866, 806, 755 cm^{-1}

EIMS (70 eV) *m/z* 648 and 646 and 644 ($M^{+\bullet}$, 1% and 2% and 1%), 633 and 631 and 629 [$(M - CH_3\bullet)^+$, 1% and 2% and 1%], 440 and 438 and 436 (8 and 16 and 8), 349 (7), 347 (7), 249 (8), 247 (8), 192 (41), 190 (43), 174 (21), 172 (21), 151 (71), 150 (80), 135 (100), 110 (40), 77 (28)

HRMS (ESI) Found: $(M + Na)^+$, 667.0138. $C_{26}H_{30}{}^{79}Br_2O_9$ requires $(M + Na)^+$, 667.0154

$[\alpha]_D$ +40.8 (*c* 1.1, $CHCl_3$)

Concentration of the filtrate derived from the fractional crystallisation of compound **136** as detailed above afforded *compound **134*** (920 mg, 55%) as a cloudy, white oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (1H, br s), 6.79 (2H, m), 6.25 (1H, d, *J* 1.7 Hz), 5.95 (2H, s), 4.66 (1H, br d, *J* 6.5 Hz), 4.62 (1H, d, *J* 11.3 Hz), 4.53 (1H, d, *J* 11.3 Hz), 4.14 (1H, dd, *J* 9.0 and 6.6 Hz), 3.86 (1H, dt, *J* 8.5 and 1.6 Hz), 3.71 (1H, t, *J* 8.8 Hz), 2.37 (1H, br s, -O*H*), 1.54 (3H, s), 1.41 (3H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9 (C), 147.4 (C), 132.9 (CH), 131.1 (C), 121.7 (CH), 118.6 (C), 111.0 (C), 108.6 (CH), 108.2 (CH), 101.1 (CH_2), 77.9 (CH), 77.5 (CH), 77.1 (CH), 72.8 (CH), 72.1 (C), 28.1 (CH_3), 25.9 (CH_3)

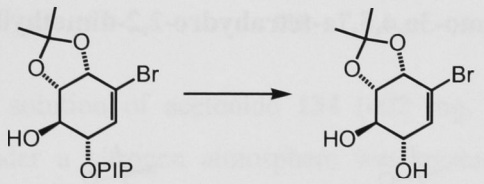
IR (thin film) ν_{max} 3454, 2988, 2933, 2890, 2036, 1850, 1733, 1644, 1608, 1503, 1490, 1444, 1381, 1251, 1219, 1163, 1071, 1039, 927, 868, 809, 732 cm^{-1}

EIMS (70 eV) *m/z* 400 and 398 ($M^{+\bullet}$, 18%), 325 and 323 (3), 192 (38), 151 (62), 135 (100), 101 (62), 77 (52), 55 (54), 43 (79)

HRMS (EI) Found: $M^{+\bullet}$, 398.0352. $C_{17}H_{19}{}^{79}BrO_6$ requires $M^{+\bullet}$, 398.0365

$[\alpha]_D$ +26.9 (*c* 1.0, $CHCl_3$)

(3a*S*,4*R*,5*S*,7a*S*)-7-Bromo-3a,4,5,7a-tetrahydro-2,2-dimethylbenzo[*d*][1,3]dioxole-4,5-diol (137)



134 **137**

A magnetically stirred solution of acetonide **134** (106 mg, 0.27 mmol) in DCM (5 mL) was treated with water (0.25 mL) and DDQ (80 mg, 0.35 mmol). The resulting solution was stirred at 18 °C for 6 h then quenched with $Na_2S_2O_5$ (1 x 10 mL of a 20% w/v aqueous solution). The separated aqueous phase was then extracted with DCM (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting brown solid was subjected to flash chromatography (silica, 2:1 v/v hexane/EtOAc elution) and concentration of the appropriate fractions (R_f 0.2 in 2:1 v/v hexane/EtOAc) afforded the previously reported diol **137**[17] (56 mg, 77%) as a white, crystalline solid.

MP 145 – 149 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (1H, d, *J* 2.6 Hz), 4.67 (1H, d, *J* 6.3 Hz), 4.20 (1H, dd, *J* 7.7 and 6.3 Hz), 4.07 (1H, m), 3.74 (1H, t, *J* 7.7 Hz), 1.53 (3H, s), 1.41 (3H, s) (signals due to the two hydroxyl proton were not observed)

^{13}C NMR (75 MHz, $CDCl_3$) δ 134.0 (CH), 119.9 (C), 111.1 (C), 77.6 (CH), 77.0 (CH), 73.0 (CH), 70.8 (CH), 28.0 (CH_3), 26.0 (CH_3)

IR (thin film) ν_{max} 3421, 2926, 2855, 1645, 1376, 1250, 1068, 869 cm^{-1}

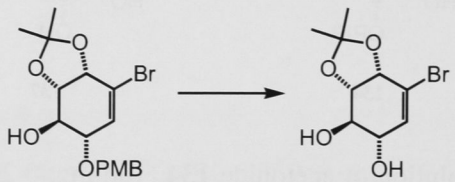
EIMS (70 eV) *m/z* 266 and 264 ($M^{+\bullet}$, <1%), 251 and 249 [$(M - CH_3\bullet)^+$, 100%], 191 (24), 110 (86), 81 (86), 69 (97)

HRMS (EI) Found: $(M - CH_3\bullet)^+$, 248.9762. $C_9H_{13}{}^{79}BrO_4$ requires $(M - CH_3\bullet)^+$, 248.9762

$[\alpha]_D$ –21.9 (*c* 1.1, MeOH)

The spectroscopic data obtained on the material prepared as described above were in good agreement with those reported previously for compound **137**.[17]

(3a*S*,4*R*,5*S*,7a*S*)-7-Bromo-3a,4,5,7a-tetrahydro-2,2-dimethylbenzo[*d*][1,3]dioxole-4,5-diol (137)

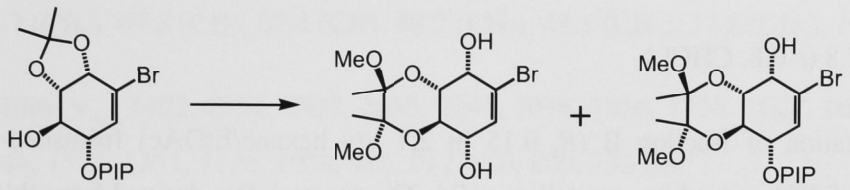


120 **137**

A magnetically stirred solution of acetonide **120** (111 mg, 0.29 mmol) in DCM (5 mL) was treated with water (0.25 mL) and DDQ (85 mg, 0.37 mmol). The resulting solution was stirred at 18 °C for 2.5 h then quenched with $Na_2S_2O_5$ (1 x 10 mL of a 20% w/v aqueous solution). The separated aqueous phase was extracted with DCM (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting brown solid was subjected to flash chromatography (silica, 2:1 v/v hexane/EtOAc elution) and concentration of the appropriate fractions (R_f 0.2 in 2:1 v/v hexane/EtOAc) afforded the previously reported diol **137**[17] (62 mg, 81%) as a white, crystalline solid.

The spectral data derived from this material were in good agreement with those obtained from the sample of compound **137** prepared as described on page 135.

(2*S*,3*S*,4a*R*,5*S*,8*S*,8a*R*)-6-Bromo-2,3,4a,5,8,8a-hexahydro-2,3-dimethoxy-2,3-dimethylbenzo[*b*][1,4]dioxine-5,8-diol (133) and (2*S*,3*S*,4a*R*,5*S*,8*S*,8a*R*)-8-((benzo[*d*][1,3]dioxol-5-yl)methoxy)-6-bromo-2,3,4a,5,8,8a-hexahydro-2,3-dimethoxy-2,3-dimethylbenzo[*b*][1,4]dioxin-5-ol (138)



134 **133** **138**

A magnetically stirred solution of acetonide **134** (402 mg, 1.01 mmol) in MeOH (20 mL) maintained under a nitrogen atmosphere was treated with 2,3-butanedione (118 mg, 1.37 mmol), trimethylorthoformate (427 mg, 4.03 mmol) and camphorsulfonic acid (12 mg, 0.05 mmol). The reaction vessel was sealed and heated to 40 °C for 118 h after which time the resulting mixture was cooled, diluted with DCM (50 mL) and washed with $NaHCO_3$ (1 x 50 mL of a saturated aqueous solution) then water (1 x 50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure, and the resulting white solid subjected to flash chromatography (silica, 10:1 → 1:1 v/v hexane/EtOAc gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f 0.5 in 2:1 v/v hexane/EtOAc) furnished *compound **138*** (180 mg, 38%) as an opaque, low-melting solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (1H, m), 6.78 – 6.77 (2H, complex m), 6.13 (1H, d, *J* 2.3 Hz), 5.94 (2H, s), 4.72 (1H, d, *J* 11.4 Hz), 4.59 (1H, d, *J* 11.4 Hz), 4.31 (1H, d, *J* 4.1 Hz), 4.15 (1H, dd, *J* 10.9 and 7.9 Hz), 4.05 (1H, dd, *J* 7.9 and 2.3 Hz), 3.71 (1H, dd, *J* 10.9 and 4.1 Hz), 3.31 (3H, s), 3.27 (3H, s), 1.34 (6H, s) (signal due to the hydroxyl proton was not observed)

^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6 (C), 147.1 (C), 132.6 (CH), 132.0 (C), 122.0 (C), 121.1 (CH), 108.4 (CH), 108.0 (CH), 100.9 (CH_2), 99.8 (C), 99.0 (C), 77.0 (CH), 72.6 (CH_2), 71.8 (CH), 67.8 (CH), 67.5 (CH), 48.1 (CH_3), 48.0 (CH_3), 17.8 (CH_3), 17.6 (CH_3)

IR (thin film) ν_{max} 3480, 2993, 2948, 2900, 2834, 2067, 1859, 1719, 1640, 1503, 1491, 1444, 1377, 1251, 1138, 1038, 926, 851, 809 cm^{-1}

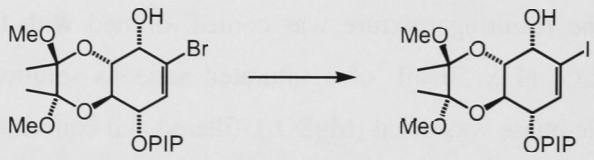
ESI-MS (positive ion mode) *m/z* 497 and 495 [$(M + Na)^+$, 33%], 492 and 490 (9), 443 and 441 (15), 135 (100)

HRMS (ESI, positive ion mode) Found: $(M + Na)^+$, 495.0626. $C_{20}H_{25}{}^{79}BrO_8$ requires $(M + Na)^+$, 495.0630

$[\alpha]_D$ +67.8 (*c* 0.8, $CHCl_3$)

Concentration of fraction B (R_f 0.15 in 2:1 v/v hexane/EtOAc) furnished *diol* ***133*** (113 mg, 33%) as a white, crystalline solid. The spectral data derived from this material were in good agreement with those obtained from the sample of compound **133** prepared as described on page 131.

(2*S*,3*S*,4a*R*,5*S*,8*S*,8a*R*)-8-((Benzo[*d*][1,3]dioxol-5-yl)methoxy)-6-iodo-2,3,4a,5,8,8a-hexahydro-2,3-dimethoxy-2,3-dimethylbenzo[*b*][1,4]dioxin-5-ol (135)



138 **135**

A magnetically stirred solution of alkenyl bromide **138** (277 mg, 0.59 mmol) in *n*-BuOH (4 mL) maintained under a nitrogen atmosphere was treated with sodium iodide (132 mg, 0.88 mmol), cuprous iodide (12 mg, 0.06 mmol) and *N*,*N*'-dimethylethylenediamine (8 mg, 0.09 mmol). The reaction vessel was then sealed and heated to 120 °C for 26 h, after which time the resulting mixture was cooled and diluted with DCM (20 mL) then washed with NH_4Cl (1 x 20 mL of a saturated aqueous solution) and brine (1 x 20 mL). The separated organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure and the resulting brown oil subjected to flash chromatography (silica, 5:1 v/v hexane/EtOAc elution). Concentration of the appropriate fractions (R_f 0.5 in 2:1 v/v hexane/EtOAc) afforded *alkenyl iodide* ***135*** (264 mg, 87% yield) as an opaque, pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (1H, br s), 6.80 – 6.74 (2H, complex m), 6.39 (1H, d, *J* 2.3 Hz), 5.95 (2H, s), 4.72 (1H, d, *J* 11.4 Hz), 4.59 (1H, d, *J* 11.4 Hz), 4.33 (1H, d, *J* 4.1 Hz), 4.13 (1H, dd, *J* 10.9 and 8.0 Hz), 4.02 (1H, dd, *J* 8.0 and 2.5 Hz), 3.73 (1H,

dd, *J* 10.9 and 4.1 Hz), 3.31 (3H, s), 3.27 (3H, s), 1.34 (6H, s) (signal due to the hydroxyl proton was not observed)

^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7 (C), 147.1 (C), 140.8 (CH), 132.1 (C), 121.2 (CH), 108.4 (CH), 108.0 (CH), 101.0 (CH_2), 99.8 (C), 99.0 (C), 96.5 (C), 78.4 (CH), 74.5 (CH), 72.7 (CH_2), 67.8 (CH), 67.4 (CH), 48.2 (CH_3), 48.1 (CH_3), 17.8 (CH_3), 17.6 (CH_3)

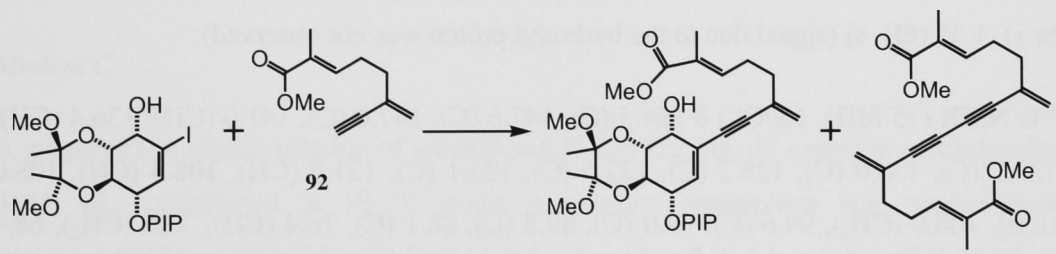
IR (thin film) ν_{max} 3492, 2992, 2927, 2835, 2247, 2038, 1856, 1716, 1627, 1609, 1503, 1491, 1444, 1377, 1251, 1136, 1038, 986, 912, 850, 809, 733 cm^{-1}

EIMS (70 eV) *m/z* 520 ($M^{+\bullet}$, 4%), 489 (3%), 372 (13), 249 (4), 150 (7), 135 (100), 123 (5), 101 (9), 77 (9), 43 (18)

HRMS (EI) Found: $M^{+\bullet}$, 520.0596. $C_{20}H_{25}IO_8$ requires $M^{+\bullet}$, 520.0594

$[\alpha]_D$ +73.2 (*c* 0.6, $CHCl_3$)

Dimethyl (2*E*,14*E*)-2,15-dimethyl-6,11-dimethylenehexadeca-2,14-dien-7,9-diynedioate (96) and methyl (2*E*)-8-((2*S*,3*S*,4a*R*,5*S*,8*R*,8a*R*)-5-((benzo[*d*][1,3]dioxol-6-yl)methoxy)-2,3,4a,5,8,8a-hexahydro-8-hydroxy-2,3-dimethoxy-2,3-dimethylbenzo[*b*][1,4]dioxin-7-yl)-2-methyl-6-methyleneoct-2-en-7-ynoate (139)



135 **139** **96**

Method A

A magnetically stirred solution of alkenyl iodide **135** (18 mg, 35 μmol) in THF (0.5 mL), maintained at 0 °C under a nitrogen atmosphere, was treated with diisopropylamine (18 mg, 0.17 mmol), dichloro*bis*(triphenylphosphine)palladium (2 mg, 2.8 μmol) and cuprous iodide (1 mg, 5.3 μmol). The resulting mixture was treated, dropwise, with a solution of alkyne **92** (8 mg, 44 μmol) in THF (0.25 mL) and stirred for 1.5 h before being diluted with DCM (10 mL) and washed with water (1 x

10 mL). The separated organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure and the resulting yellow oil was subjected to flash chromatography (silica, 5:1 → 2:1 v/v hexane/EtOAc gradient elution) to give three fractions, A, B and C.

Concentration of fraction A (R_f 0.5 in 5:1 v/v hexane/EtOAc) afforded *alkyne dimer* ***96*** (1 mg, 32%) as a clear, colourless oil. The spectral data derived from this material were in good agreement with those obtained from the sample of compound **96** prepared as described on page 109.

Concentration of fraction B (R_f 0.2 in 5:1 v/v hexane/EtOAc) afforded *starting material* ***135*** (13 mg, 70% recovery) as a pale-yellow oil. The spectroscopic data obtained on this material were in good agreement with those recorded earlier for compound **135**.

Concentration of fraction C (R_f 0.1 in 5:1 v/v hexane/EtOAc) afforded *cross-coupled product* ***139*** (5 mg, 24%) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (1H, br s), 6.81 – 6.71 (3H, complex m), 6.07 (1H, d, *J* 2.5 Hz), 5.92 (2H, s), 5.38 (1H, d, *J* 1.4 Hz), 5.29 (1H, d, *J* 1.2 Hz), 4.75 (1H, d, *J* 11.4 Hz), 4.61 (1H, d, *J* 11.6 Hz), 4.24 – 4.13 (3H, complex m), 3.72 (3H, s), 3.63 (1H, dd, *J* 10.3 and 3.8 Hz), 3.32 (3H, s), 3.28 (3H, s), 2.42 (2H, m), 2.30 (2H, m), 1.84 (3H, br s), 1.35 (6H, s) (signal due to the hydroxyl proton was not observed)

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5 (C), 147.6 (C), 147.0 (C), 141.0 (CH), 136.4 (CH), 132.3 (C), 130.0 (C), 128.2 (C), 122.6 (C), 122.1 (C), 121.0 (CH), 108.4 (CH), 108.0 (CH), 100.9 (CH_2), 99.6 (C), 99.0 (C), 89.8 (C), 88.1 (C), 76.4 (CH), 72.5 (CH_2), 68.4 (CH), 68.2 (CH), 67.6 (CH), 51.7 (CH_3), 48.1 (CH_3), 48.0 (CH_3), 35.9 (CH_2), 27.3 (CH_2), 17.9 (CH_3), 17.6 (CH_3), 12.5 (CH_3)

IR (thin film) ν_{max} 3416, 2992, 2949, 2901, 1713, 1649, 1503, 1491, 1443, 1376, 1250, 1141, 1120, 1082, 1038, 927 cm^{-1}

ESI-MS (positive ion mode) *m/z* 593 [$(M + Na)^+$, 100%]

HRMS (ESI, positive ion mode) Found: $(M + Na)^+$, 593.2375. $C_{31}H_{38}O_{10}$ requires $(M + Na)^+$, 593.2363

$[\alpha]_D$ +76.2 (*c* 0.6, $CHCl_3$)

Method B

A magnetically stirred solution of alkenyl iodide **135** (39 mg, 75 μmol) in piperidine (0.2 mL) maintained under a nitrogen atmosphere was treated with alkyne **92** (20 mg, 0.12 mmol) and dichloro*bis*(triphenylphosphine)palladium (8 mg, 11 μmol) before being placed in a pre-heated 70 °C oil bath for 1.75 h. The cooled reaction mixture was diluted with DCM (10 mL) then washed with NH_4Cl (1 x 10 mL of a saturated aqueous solution) and brine (1 x 10 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 10:1 → 2:1 v/v hexane/EtOAc gradient elution) to give two fractions, A and B.

Concentration of fraction A (R_f 0.2 in 5:1 v/v hexane/EtOAc) afforded *starting material **135*** (16 mg, 41% recovery) as a pale-yellow oil. The spectroscopic data obtained on this material were in good agreement with those recorded earlier for compound **135**.

Concentration of fraction B (R_f 0.1 in 5:1 v/v hexane/EtOAc) afforded *cross-coupled product **139*** (22 mg, 52%) as a pale-yellow oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **139** prepared by Method A.

Method C

A magnetically stirred solution of alkenyl iodide **135** (22 mg, 42 μmol) in triethylamine (0.15 mL) maintained at 18 °C under a nitrogen atmosphere was treated with *tris*(dibenzylideneacetone)dipalladium (1 mg, 1 μmol) and tri-*t*-butylphosphine (3 μL of a 10% w/v solution in triethylamine, 1.5 μmol). The resulting mixture was then treated, dropwise, with a solution of alkyne **92** (13 mg, 73 μmol) in triethylamine (0.15 mL). The ensuing black solution was stirred for an additional 25 h before being diluted with DCM (10 mL) and washed with water (1 x 10 mL). The separated organic phase was dried ($MgSO_4$), filtered, then concentrated under reduced pressure and the resulting brown oil subjected to flash chromatography (silica, 5:1 → 2:1 v/v hexane/EtOAc gradient elution) to give two fractions, A and B.

Concentration of fraction A (R_f 0.2 in 5:1 v/v hexane/EtOAc) afforded *starting material* ***135*** (6 mg, 27% recovery) as a pale-yellow oil. The spectroscopic data obtained on this material were in good agreement with those recorded earlier for compound **135**.

Concentration of fraction B (R_f 0.1 in 5:1 v/v hexane/EtOAc) afforded *cross-coupled product* ***139*** (5 mg, 20%) as a pale-yellow oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **139** prepared by Method A.

Method D

A magnetically stirred solution of alkenyl iodide **135** (21 mg, 41 μmol) in 1:1:2.5 v/v/v *N*,*N*-dimethylformamide/triethylamine/*N*,*N*-dimethylacetamide (0.9 mL) maintained under a nitrogen atmosphere was treated, sequentially, with alkyne **92** (10 mg, 56 μmol), triphenylphosphine (2 mg, 8 μmol) and palladium diacetate (2 mg, 9 μmol). The resulting mixture was stirred at 18 °C for 6 h before being diluted with DCM (15 mL) and washed with water (3 x 10 mL) and brine (1 x 10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a brown oil that was subjected to flash chromatography (silica, 5:1 → 2:1 v/v hexane/EtOAc gradient elution) to give two fractions, A and B.

Concentration of fraction A (R_f 0.2 in 5:1 v/v hexane/EtOAc) afforded *starting material* ***135*** (9 mg, 42% recovery) as a pale-yellow oil. The spectroscopic data obtained on this material were in good agreement with those recorded earlier for compound **135**.

Concentration of fraction B (R_f 0.1 in 5:1 v/v hexane/EtOAc) afforded *cross-coupled product* ***139*** (10 mg, 42%) as a pale-yellow oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **139** prepared by Method A.

Method E

A solution of alkenyl iodide **135** (21 mg, 40 μmol) in acetone (0.3 mL) maintained under a nitrogen atmosphere was treated, sequentially, with alkyne **139** (10 mg, 57 μmol), palladium dichloride (1 mg, 3 μmol) and triethylamine (6 mg, 57 μmol). The resulting solution was subjected to ultrasound irradiation for 3 h whilst maintaining the

water bath temperature below 30 °C. The resulting mixture was diluted with DCM (10 mL) then washed with NH_4Cl (1 x 10 mL of a saturated aqueous solution) and brine (1 x 10 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure and the resulting brown oil was subjected to flash chromatography (silica, 5:1 → 2:1 v/v hexane/EtOAc gradient elution) give three fractions, A, B and C.

Concentration of fraction A (R_f 0.5 in 5:1 v/v hexane/EtOAc) afforded *alkyne dimer* ***96*** (2 mg, 22%) as a clear, colourless oil. The spectral data derived from this material were in good agreement with those obtained from the sample of compound **96** prepared as described on page 109.

Concentration of fraction B (R_f 0.2 in 5:1 v/v hexane/EtOAc) afforded *starting material* ***135*** (3 mg, 14% recovery) as a pale-yellow oil. The spectroscopic data obtained on this material were in good agreement with those recorded earlier for compound **135**.

Concentration of fraction C (R_f 0.1 in 5:1 v/v hexane/EtOAc) afforded *cross-coupled product* ***139*** (7 mg, 32%) as a pale-yellow oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **139** prepared by Method A.

Method F

A magnetically stirred solution of alkenyl iodide **135** (19 mg, 37 μmol) in pyrrolidine (0.15 mL) maintained at 18 °C under a nitrogen atmosphere was treated with alkyne **92** (11 mg, 62 μmol) and *tetrakis*(triphenylphosphine)palladium (2 mg, 2 μmol). The resulting mixture was stirred for 48 h at 18 °C before being diluted with DCM (15 mL) then washed with NH_4Cl (1 x 10 mL of a saturated aqueous solution) and brine (1 x 10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a bright-yellow oil that was subjected to flash chromatography (silica, 5:1 → 2:1 v/v hexane/EtOAc gradient elution) to give two fractions, A and B.

Concentration of fraction A (R_f 0.2 in 5:1 v/v hexane/EtOAc) afforded *starting material* ***135*** (14 mg, 73% recovery) as a pale-yellow oil. The spectroscopic data obtained on this material were in good agreement with those recorded earlier for compound **135**.

Concentration of fraction B (R_f 0.1 in 5:1 v/v hexane/EtOAc) afforded *cross-coupled product* ***139*** (3 mg, 12%) as a pale-yellow oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **139** prepared by Method A.

Method G

A magnetically stirred solution of alkenyl iodide **135** (20 mg, 39 μmol) in EtOAc (0.25 mL) maintained under a nitrogen atmosphere was treated, sequentially, with diisopropylamine (16 mg, 0.16 mmol), dichloro*bis*(triphenylphosphine)palladium (1 mg, 1.9 μmol) and cuprous iodide (1 mg, 2.6 μmol). The resulting mixture was degassed then cooled to *ca.* –10 °C and treated, over 2 h, with a degassed solution of alkyne **92** (11 mg, 61 μmol) in EtOAc (0.2 mL). The ensuing solution was stirred for 0.5 h before being quenched with NH_4Cl (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with DCM (1 x 10 mL) and the combined organic phases washed with brine (1 x 10 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 5:1 → 2:1 v/v hexane/EtOAc gradient elution) to give two fractions, A and B.

Concentration of fraction A (R_f 0.2 in 5:1 v/v hexane/EtOAc) afforded *starting material* ***135*** (3 mg, 16% recovery) as a pale-yellow oil. The spectroscopic data obtained on this material were in good agreement with those recorded earlier for compound **135**.

Concentration of fraction B (R_f 0.1 in 5:1 v/v hexane/EtOAc) afforded *cross-coupled product* ***139*** (15 mg, 69%) as a pale-yellow oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **139** prepared by Method A.

Method H – small-scale procedure

A magnetically stirred solution of alkenyl iodide **135** (20 mg, 39 μmol) in piperidine (0.1 mL) maintained under a nitrogen atmosphere was treated with dichloro*bis*(triphenylphosphine)palladium (2 mg, 2.9 μmol) and the resulting solution stirred at 18 °C for 2.5 h. Meanwhile, a magnetically stirred solution of alkyne **92** (11 mg, 61 μmol) in piperidine (0.3 mL) maintained under a nitrogen atmosphere was

treated with indium trichloride (1 mg, 2.3 μmol) and the resulting slurry stirred at 18 °C for 2.5 h. The slurry containing alkyne **92** was treated, sequentially, with the solution containing alkenyl iodide **135** and piperidine (0.1 mL). The reaction vessel was sealed and heated to 60 °C for 4 h then the reaction mixture was cooled and diluted with DCM (10 mL). It was then washed with NH_4Cl (1 x 10 mL of a saturated aqueous solution) and brine (1 x 10 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting bright-yellow oil was subjected to flash chromatography (silica, 5:1 → 2:1 v/v hexane/EtOAc gradient elution) to give two fractions, A and B.

Concentration of fraction A (R_f 0.2 in 5:1 v/v hexane/EtOAc) afforded *starting material **135*** (5 mg, 24% recovery) as a pale-yellow oil. The spectroscopic data obtained on this material were in good agreement with those recorded earlier for compound **135**.

Concentration of fraction B (R_f 0.1 in 5:1 v/v hexane/EtOAc) afforded *cross-coupled product **139*** (16 mg, 71%) as a pale-yellow oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **139** prepared by Method A.

Method H – "large-scale" procedure

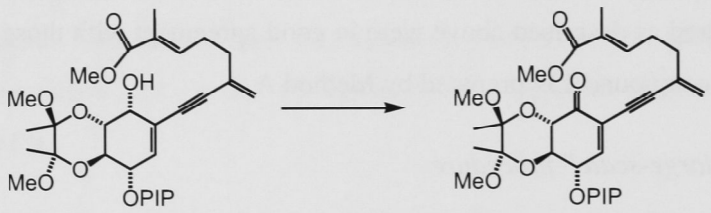
A magnetically stirred solution of alkenyl iodide **135** (479 mg, 0.92 mmol) in piperidine (1 mL) maintained under a nitrogen atmosphere was treated with dichloro*bis*(triphenylphosphine)palladium (33 mg, 47 μmol) and the resulting solution stirred at 18 °C for 0.75 h. Meanwhile, a magnetically stirred solution of alkyne **92** (238 mg, 1.34 mmol) in piperidine (2 mL) maintained under a nitrogen atmosphere was treated with indium trichloride (44 mg, 0.20 mmol) and the resulting slurry stirred at 18 °C for 0.75 h. The slurry containing alkyne **92** was then treated, sequentially, with the solution containing alkenyl iodide **135** and piperidine (2 mL). The reaction vessel was sealed and heated to 60 °C for 8 h, then the resulting reaction mixture was cooled, diluted with DCM (50 mL) and then washed with HCl (1 x 50 mL of a 0.5 M aqueous solution), $NaHCO_3$ (1 x 50 mL of a saturated aqueous solution) and brine (1 x 10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a bright-yellow oil that was subjected to flash chromatography (silica, 10:1 → 2:1 v/v hexane/EtOAc gradient elution) to give two fractions, A and B.

Concentration of fraction A (R_f 0.2 in 5:1 v/v hexane/EtOAc) afforded *starting material* ***135*** (51 mg, 11% recovery) as a pale-yellow oil. The spectroscopic data obtained on this material were in good agreement with those recorded earlier for compound **135**.

Concentration of fraction B (R_f 0.1 in 5:1 v/v hexane/EtOAc) afforded *cross-coupled product* ***139*** (424 mg, 81%) as a pale-yellow oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **139** prepared by Method A.

5.5 Experimental Procedures Associated with Work Described in Chapter Four

Methyl (2*E*)-8-((2*S*,3*S*,4a*R*,5*S*,8a*S*)-5-(2-(benzo[*d*][1,3]dioxol-6-yl)ethyl)-2,3,4a,5,8,8a-hexahydro-2,3-dimethoxy-2,3-dimethyl-8-oxobenzo[*b*][1,4]dioxin-7-yl)-2-methyl-6-methyleneoct-2-en-7-ynoate (140)



139 **140**

A magnetically stirred solution of alcohol **139** (60 mg, 0.11 mmol) in DCM (5 mL) maintained at 0 °C under a nitrogen atmosphere was treated with Dess-Martin periodinane (81 mg, 0.19 mmol). The resulting slurry was stirred at 0 → 18 °C for 18 h before being diluted with DCM (10 mL) and washed with $NaHCO_3$ (3 x 10 mL of a saturated aqueous solution). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure and the resulting yellow oil was subjected to flash chromatography (silica, 5:1 → 1:1 v/v hexane/EtOAc gradient elution). Concentration of the appropriate fractions (R_f 0.6 in 2:1 v/v hexane/EtOAc) afforded the *title ketone* ***140*** (33 mg, 55%) as a viscous, yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (1H, d, *J* 2.5 Hz), 6.90 (1H, m), 6.84 – 6.77 (2H, complex m), 6.71 (1H, tq, *J* 7.2 and 1.5 Hz), 5.96 (2H, s), 5.43 (1H, m), 5.34 (1H, m), 4.83 (1H, d, *J* 11.5 Hz), 4.69 (1H, d, *J* 11.5 Hz), 4.46 (1H, dd, *J* 8.4 and 2.5 Hz), 4.27

(1H, d, *J* 11.4 Hz), 4.13 (1H, dd, *J* 11.4 and 8.4 Hz), 3.72 (3H, s), 3.30 (3H, s), 3.29 (3H, s), 2.45 (2H, m), 2.31 (2H, m), 1.84 (3H, m), 1.41 (3H, s), 1.37 (3H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4 (C), 168.6 (C), 149.1 (CH), 147.8 (C), 147.4 (C), 140.9 (CH), 131.8 (C), 129.8 (C), 128.3 (C), 123.9 (C), 123.5 (C), 121.5 (CH), 108.5 (CH), 108.1 (CH), 101.1 (CH_2), 100.1 (C), 99.0 (C), 94.0 (C), 82.4 (C), 75.3 (CH), 73.9 (CH), 73.6 (CH), 71.9 (CH_2), 51.7 (CH_3), 48.5 (CH_3), 48.1 (CH_3), 35.8 (CH_2), 27.1 (CH_2), 17.6 (CH_3), 17.5 (CH_3), 12.5 (CH_3)

IR (thin film) ν_{max} 2995, 2950, 1714, 1503, 1491, 1444, 1378, 1251, 1139, 1037, 755 cm^{-1}

ESI-MS (positive ion mode) *m/z* 591 [$(M + Na)^+$, 27%], 135 (100)

HRMS (ESI, positive ion mode) Found: $(M + Na)^+$, 591.2207. $C_{31}H_{36}O_{10}$ requires $(M + Na)^+$, 591.2206

$[\alpha]_D$ +130.4 (*c* 0.6, $CHCl_3$)

(2*E*)-8-((2*S*,3*S*,4a*R*,5*S*,8*R*,8a*R*)-5-((Benzo[*d*][1,3]dioxol-6-yl)methoxy)-2,3,4a,5,8,8a-hexahydro-8-hydroxy-2,3-dimethoxy-2,3-dimethylbenzo[*b*][1,4]dioxin-7-yl)-2-methyl-6-methyleneoct-2-en-7-ynoic acid (142)

139 **142**

A magnetically stirred solution of methyl ester **139** (303 mg, 0.53 mmol) in THF/MeOH (8 mL of a 1:1 v/v solution) was treated with a solution of lithium hydroxide monohydrate (235 mg, 5.60 mmol, in 2 mL water). The ensuing mixture was stirred at 18 °C for 18 h before being diluted with DCM (20 mL) and then the aqueous layer acidified to *ca.* pH 3 with HCl (2 M aqueous solution). The separated aqueous phase was washed with DCM (4 x 20 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting white solid

was subjected to flash chromatography (silica, 1:1 v/v hexane/EtOAc elution) and concentration of the relevant fractions (R_f 0.1 in 2:1 hexane/EtOAc) afforded *carboxylic acid* ***142*** (200 mg, 71%) as a cream-coloured and low-melting solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 – 6.84 (2H, complex m), 6.81 – 6.74 (2H, complex m), 6.07 (1H, d, *J* 2.5 Hz), 5.94 (2H, s), 5.38 (1H, d, *J* 1.6 Hz), 5.29 (1H, d, *J* 1.4 Hz), 4.74 (1H, d, *J* 11.4 Hz), 4.61 (1H, d, *J* 11.5 Hz), 4.23 – 4.14 (3H, complex m), 3.63 (1H, dd, *J* 10.6 and 4.1 Hz), 3.31 (3H, s), 3.27 (3H, s), 2.44 (2H, m), 2.31 (2H, m), 1.85 (3H, m), 1.34 (6H, s) (signals due to the hydroxyl and carboxylic acid protons were not observed)

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 147.7 (C), 147.0 (C), 143.5 (CH), 136.5 (CH), 132.4 (C), 129.9 (C), 127.6 (C), 122.8 (C), 122.1 (C), 121.1 (CH_2), 108.4 (CH), 108.0 (CH), 100.9 (CH_2), 99.7 (C), 99.1 (C), 89.7 (C), 88.2 (C), 76.4 (CH), 72.6 (CH_2), 68.4 (CH), 68.2 (CH), 67.6 (CH), 48.11 (CH_3), 48.05 (CH_3), 35.8 (CH_2), 27.6 (CH_2), 17.9 (CH_3), 17.6 (CH_3), 12.2 (CH_3)

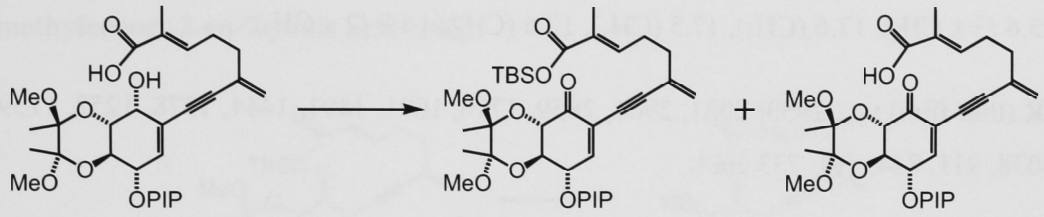
IR (thin film) ν_{max} 3448, 2992, 2948, 1687, 1491, 1444, 1376, 1250, 1140, 1038, 926, 808 cm^{-1}

ESI-MS (positive ion mode) *m/z* 579 [$(M + Na)^+$, 100%]

HRMS (ESI, positive ion mode) Found: $(M + Na)^+$, 579.2216. $C_{30}H_{36}O_{10}$ requires $(M + Na)^+$, 579.2206

$[\alpha]_D$ +87.4 (*c* 0.2, $CHCl_3$)

(2*E*)-8-((2*S*,3*S*,4a*R*,5*S*,8a*S*)-5-((Benzo[*d*][1,3]dioxol-6-yl)methoxy)-2,3,4a,5,8,8a-hexahydro-2,3-dimethoxy-2,3-dimethyl-8-oxobenzo[*b*][1,4]dioxin-7-yl)-2-methyl-6-methyleneoct-2-en-7-ynoic acid (141) and (2*E*)-*tert*-butyldimethylsilyl 8-((2*S*,3*S*,4a*R*,5*S*,8a*S*)-5-((benzo[*d*][1,3]dioxol-6-yl)methoxy)-2,3,4a,5,8,8a-hexahydro-2,3-dimethoxy-2,3-dimethyl-8-oxobenzo[*b*][1,4]dioxin-7-yl)-2-methyl-6-methyleneoct-2-en-7-ynoate (143)



142 **143** **141**

A magnetically stirred solution of carboxylic acid **142** (55 mg, 0.10 mmol) in THF (2 mL) maintained at 18 °C under a nitrogen atmosphere was treated with imidazole (20 mg, 0.30 mmol) and *t*-butyldimethylchlorosilane (30 mg, 0.20 mmol). The resulting solution was stirred for 1.5 h before being diluted with DCM (15 mL) and washed with water (1 x 15 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. A magnetically stirred solution of the resulting pale-yellow oil in DCM (2 mL), maintained at 0 °C under a nitrogen atmosphere, was treated with pyridine (74 μL, 0.74 mmol) and Dess-Martin periodinane (74 mg, 0.18 mmol). The resulting slurry was stirred at 0 → 18 °C for 16 h before being diluted with DCM (20 mL), washed with $NaHCO_3$ (2 x 20 mL of a saturated aqueous solution) and brine (1 x 20 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 10:1 → 2:1 v/v hexane/EtOAc gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f 0.7 in 2:1 v/v hexane/EtOAc) afforded *TBDMS-ketone **143*** (18 mg, 27%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (1H, d, *J* 2.5 Hz), 6.90 (1H, m), 6.84 – 6.77 (2H, complex m), 6.72 (1H, tq, *J* 7.3 and 1.4 Hz), 5.96 (2H, s), 5.43 (1H, d, *J* 1.5 Hz), 5.33 (1H, d, *J* 1.4 Hz), 4.83 (1H, d, *J* 11.4 Hz), 4.69 (1H, d, *J* 11.4 Hz), 4.46 (1H, dd, *J* 8.4 and 2.5 Hz), 4.27 (1H, d, *J* 11.4 Hz), 4.13 (1H, dd, *J* 11.3 and 8.4 Hz), 3.30 (3H, s),

3.29 (3H, s), 2.44 (2H, m), 2.31 (2H, m), 1.82 (3H, d, *J* 1.4 Hz), 1.41 (3H, s), 1.36 (3H, s), 0.94 (9H, s), 0.28 (6H, s)

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4 (C), 168.2 (C), 149.1 (CH), 147.8 (C), 147.4 (C), 141.6 (CH), 131.5 (C), 129.8 (CH_2), 129.7 (C), 123.9 (C), 123.4 (C), 121.5 (CH), 108.5 (CH), 108.1 (CH), 101.1 (CH_2), 100.1 (C), 99.0 (C), 94.0 (C), 82.3 (C), 75.3 (CH), 73.9 (CH_2), 73.6 (CH), 71.9 (CH), 48.4 (CH_3), 48.1 (CH_3), 35.9 (CH_2), 29.7 (C), 27.2 (CH_2), 25.6 (3 x CH_3), 17.6 (CH_3), 17.5 (CH_3), 12.6 (CH_3), –4.8 (2 x CH_3)

IR (thin film) ν_{max} 2953, 2931, 2901, 2859, 1716, 1691, 1491, 1444, 1378, 1252, 1139, 1038, 911, 844, 791, 733 cm^{-1}

ESI-MS (positive ion mode) *m/z* 691 [$(M + Na)^+$, 96%], 669 ($M^{+\bullet}$, 16%), 605 (100), 577 (46), 135 (48)

HRMS (ESI, positive ion mode) Found: $(M + Na)^+$, 691.2933. $C_{36}H_{48}O_{10}Si$ requires $(M + Na)^+$, 691.2914

$[\alpha]_D$ +89.4 (*c* 0.5, $CHCl_3$)

Concentration of fraction B (R_f 0.1 in 2:1 v/v hexane/EtOAc) afforded *ketone* ***141*** (25 mg, 46%) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (1H, d, *J* 2.3 Hz), 6.90 (1H, m), 6.86 (1H, m), 6.80 (2H, m), 5.96 (2H, s), 5.44 (1H, br s), 5.34 (1H, br s), 4.83 (1H, d, *J* 11.4 Hz), 4.70 (1H, d, *J* 11.4 Hz), 4.46 (1H, dd, *J* 8.4 and 2.5 Hz), 4.27 (1H, d, *J* 11.4 Hz), 4.13 (1H, dd, *J* 11.4 and 8.4 Hz), 3.30 (3H, s), 3.29 (3H, s), 2.48 (2H, m), 2.34 (2H, m), 1.86 (3H, br s), 1.41 (3H, s), 1.36 (3H, s) (signal due to the carboxylic acid proton was not observed)

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4 (C), 171.7 (C), 149.2 (CH), 147.8 (C), 147.4 (C), 143.4 (CH), 131.9 (C), 131.6 (C), 129.7 (CH_2), 123.9 (C), 123.6 (C), 121.5 (CH), 108.6 (CH), 108.1 (CH), 101.1 (CH_2), 100.1 (C), 99.0 (C), 94.0 (C), 82.5 (C), 75.3 (CH), 73.9 (CH_2), 73.6 (CH), 71.9 (CH), 48.5 (CH_3), 48.1 (CH_3), 35.7 (CH_2), 27.4 (CH_2), 17.7 (CH_3), 17.5 (CH_3), 14.1 (CH_3)

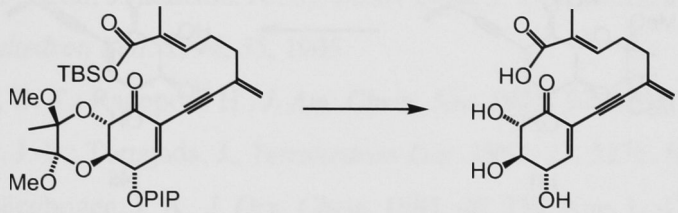
IR (thin film) ν_{max} 2959, 2956, 2855, 2665, 1714, 1689, 1491, 1445, 1378, 1256, 1139, 1117, 1037, 930, 806, 757 cm^{-1}

ESI-MS (positive ion mode) *m/z* 577 [(M + Na)$^+$, 100%]

HRMS (ESI, positive ion mode) Found: (M + Na)$^+$, 577.2048. $C_{30}H_{34}O_{10}$ requires (M + Na)$^+$, 577.2050

$[\alpha]_D$ +82.8 (*c* 0.4, $CHCl_3$)

(2*E*)-8-((4*S*,5*R*,6*S*)-4,5,6-Trihydroxy-1-oxocyclohex-2-enyl)-2-methyl-6-methyleneoct-2-en-7-ynoic acid (145)



143 **145**

A magnetically stirred solution of ketone **143** (21 mg, 31 μmol) in DCM (2 mL) was treated with trifluoroacetic acid/H_2O (525 μL of a 20:1 v/v solution). The resulting mixture was stirred at 18 °C for 2 h, then diluted with MeOH (5 ml) and concentrated under reduced pressure. The resulting brown solid was washed with Et_2O (4 x 5 mL) then dissolved in MeOH and filtered through a plug of glass wool. The ensuing filtrate was concentrated under reduced pressure to afford *triol **145*** (7 mg, 68%) as a brown solid.

^{1}H NMR (300 MHz, CD_3OD) δ 7.07 (1H, d, *J* 2.3 Hz), 6.76 (1H, m), 5.41 (1H, m), 5.38 (1H, br s), 4.40 (1H, dd, *J* 8.3 and 2.3 Hz), 4.05 (1H, d, *J* 11.0 Hz), 3.57 (1H, dd, *J* 11.0 and 8.4 Hz), 2.48 (2H, m), 2.35 (2H, m), 1.82 (3H, s) (signals due to the three hydroxyl protons and the carboxylic acid proton were not observed)

Satisfactory ^{13}C NMR spectral data could not be obtained on this compound

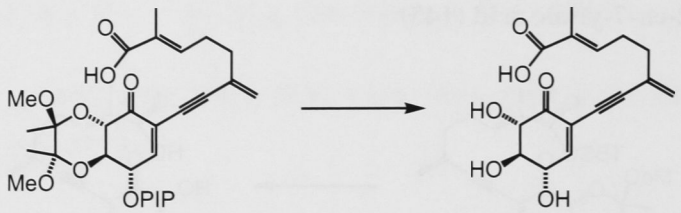
IR (thin film) ν_{max} 3375, 2924, 1693, 1502, 1483, 1437, 1387, 1260, 1137, 1037, 933, 875, 801 cm^{-1}

ESI-MS (negative ion mode) *m/z* 305 [(M – H)$^-$, 100%]

HRMS (ESI, negative ion mode) Found $(M - H)^-$, 305.1026. $C_{16}H_{18}O_6$ requires $(M - H)^-$, 305.1025

$[\alpha]_D$ +33.2 (*c* 0.5, MeOH)

(2*E*)-8-((4*S*,5*R*,6*S*)-4,5,6-Trihydroxy-1-oxocyclohex-2-enyl)-2-methyl-6-methyleneoct-2-en-7-ynoic acid (145)



141 **145**

A magnetically stirred solution of ketone **141** (15 mg, 27 μmol) in DCM (2 mL) was treated with trifluoroacetic acid/H_2O (525 μL of a 20:1 v/v solution). The resulting mixture was stirred at 18 °C for 2 h then diluted with MeOH before being concentrated under reduced pressure. The resulting brown solid was washed with Et_2O (4 x 5 mL) then dissolved in MeOH and filtered through a plug of glass wool. The ensuing filtrate was concentrated under reduced pressure to afford *triol **145*** (6 mg, 67%) as a brown solid.

The spectral data derived from this material were in good agreement with those obtained from the sample of compound **145** prepared as described on page 151.

5.6 REFERENCES

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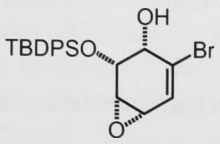
Appendix One: X-ray Crystallographic Data for Compound 124



124

Crystal data

$C_{22}H_{25}BrO_3Si$
$M_r = 445.43$
Orthorhombic
$P2_12_12_1$
$a = 11.8717\ (1)$ Å
$b = 12.2858\ (3)$ Å
$c = 14.4426\ (3)$ Å
$V = 2106.50\ (7)$ Å^3
$Z = 4$
$D_x = 1.404$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å

Cell parameters from 15862 reflections
$\theta = 2.6 - 27.5°$
$\mu = 2.027$ mm^{-1}
$T = 200$ K
Block
Colourless
0.50 x 0.47 x 0.27 mm
Crystal source: local

Data collection

Nonius KappaCCD diffractometer
φ and ω scans with CCD
Absorption correction:
by integration via Gaussian
method (Coppens, 1970)
implemented in maXus
(2000)
$T_{min} = 0.447$, $T_{max} = 0.613$
24040 measured reflections
4834 independent reflections

4171 reflections with
$I > 3.0\sigma(I)$
$R_{int} = 0.048$
$\theta_{max} = 27.507°$
$h = -15 \rightarrow 14$
$k = -15 \rightarrow 15$
$l = -18 \rightarrow 17$

Refinement

Refinement on F
$R = 0.0214$
$\omega R = 0.0246$
$S = 1.1232$
4171 reflections
321 parameters
Only coordinates of H atoms refined
Method, part 1, Chebychev polynomial,
(Carruthers & Watkin, 1979, Prince, 1982)
[weight] = $1.0/[A_0*T_0(x) + A_1*T_1(x) \ldots + A_{n-1}]*T_{n-1}(x)]$
where A_i are the Chebychev coefficients
listed below and x = Fcalc/Fmax Method

$(\Delta/\sigma)_{max} = 0.005832$
$\Delta\rho_{max} = 0.45$ e Å^{-3}
$\Delta\rho_{min} = -0.65$ e Å^{-3}
Extinction correction: Larson (1970),
Equation 22
Extinction coefficient: 270 (20)
Scattering factors from International
Tables Vol C 4.2.6.8 and 6.1.1.4
Absolute structure: Flack (1983), 2110
Friedel-pairs
Flack parameter = -0.017 (4)

= Robust Weighting (Prince, 1982) W = [weight] * [1-(deltaF/6*sigmaF)^2]^2 A_i are: 2.12 -0.830 1.63

Table 1. Selected geometric parameters (Å)

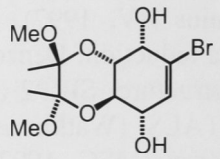
Br7—C6	1.8984 (14)	O10—C1—C2	110.58 (14)
Si11—O10	1.6526 (11)	O10—C1—C8	109.66 (13)
Si11—C12	1.8749 (16)	C2—C1—C8	111.77 (13)
Si11—C18	1.8744 (18)	C1—C2—O3	117.30 (15)
Si11—C24	1.8943 (17)	C1—C2—C4	117.62 (15)
O3—C2	1.437 (3)	O3—C2—C4	60.67 (14)
O3—C4	1.463 (3)	O3—C4—C2	58.90 (13)
O9—C8	1.423 (2)	O3—C4—C5	115.98 (17)
O10—C1	1.4177 (19)	C2—C4—C5	118.63 (16)
C1—C2	1.495 (2)	C4—C5—C6	119.53 (16)
C1—C8	1.534 (2)	Br7—C6—C5	119.95 (13)
C2—C4	1.460 (3)	Br7—C6—C8	116.65 (11)
C4—C5	1.470 (3)	C5—C6—C8	123.28 (14)
C5—C6	1.320 (2)	C1—C8—C6	108.77 (13)
C6—C8	1.511 (2)	C1—C8—O9	112.46 (14)
C12—C13	1.398 (2)	C6—C8—O9	110.50 (13)
C12—C17	1.401 (2)	Si11—C12—C13	120.63 (13)
C13—C14	1.394 (3)	Si11—C12—C17	121.40 (13)
C14—C15	1.376 (3)	C13—C12—C17	117.67 (16)
C15—C16	1.378 (3)	C12—C13—C14	120.99 (17)
C16—C17	1.393 (3)	C13—C14—C15	119.85 (17)
C18—C19	1.401 (2)	C14—C15—C16	120.70 (17)
C18—C23	1.401 (2)	C15—C16—C17	119.53 (18)
C19—C20	1.387 (3)	C12—C17—C16	121.25 (17)
C20—C21	1.373 (3)	Si11—C18—C19	118.78 (13)
C21—C22	1.374 (4)	Si11—C18—C23	124.28 (14)
C22—C23	1.388 (3)	C19—C18—C23	116.92 (17)
C24—C25	1.524 (2)	C18—C19—C20	121.28 (18)
C24—C26	1.534 (3)	C19—C20—C21	120.3 (2)
C24—C27	1.531 (3)	C20—C21—C22	120.0 (2)
		C21—C22—C23	120.0 (2)
O10—Si11—C12	106.78 (7)	C18—C23—C22	121.4 (2)
O10—Si11—C18	110.47 (7)	Si11—C24—C25	109.90 (13)
C12—Si11—C18	108.74 (7)	Si11—C24—C26	108.27 (13)
O10—Si11—C24	107.03 (7)	C25—C24—C26	108.18 (18)
C12—Si11—C24	108.12 (7)	Si11—C24—C27	112.06 (13)
C18—Si11—C24	115.34 (8)	C25—C24—C27	110.60 (17)
C2—O3—C4	60.44 (13)	C26—C24—C27	107.70 (18)
Si11—O10—C1	128.76 (11)		

Table 2. Hydrogen-bonding geometry (Å, °)

D—H···A	D—H	H···A	D···A	D—H···A
O9—H1···O3	0.87 (2)	2.04 (2)	2.796 (2)	145 (2)

All H atoms were then refined positionally.
Data collection: COLLECT (Nonius BV, 1997). Cell refinement: Denzo/Scalepack (Otwinowski & Minor, 1997). Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1997). Program(s) used to solve structure: SIR92 (Altomare *et al.* 1994). Program(s) used to refine structure: CRYSTALS (Watkin *et al.* 2003). Molecular graphics: ORTEP–II (Johnson 1976) in teXsan (MSC, 1992–1997). Software used to prepare material for publication: CRYSTALS (Watkin *et al.* 2003).

Appendix Two: X-ray Crystallographic Data for compound 124



133

Crystal data

$C_{12}H_{19}BrO_6$
$M_r = 339.18$
Orthorhombic
$P2_12_12_1$
$a = 6.69400\ (10)$ Å
$b = 13.4822\ (2)$ Å
$c = 31.8122\ (5)$ Å
$V = 2871.05\ (8)$ Å^3
$Z = 8$
$D_x = 1.569$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å

Cell parameters from 15862 reflections
$\theta = 3 - 27.5°$
$\mu = 2.833$ mm^{-1}
$T = 200$ K
Plate
Colourless
0.26 x 0.24 x 0.04 mm
Crystal source: local

Data collection

Nonius KappaCCD diffractometer
φ and ω scans with CCD
Absorption correction:
by integration via Gaussian
method (Coppens, 1970)
implemented in maXus
(2000)
$T_{min} = 0.616$, $T_{max} = 0.892$
33697 measured reflections
6582 independent reflections

4375 reflections with
$I > 3.0\sigma(I)$
$R_{int} = 0.060$
$\theta_{max} = 27.474°$
$h = -8 \rightarrow 8$
$k = -17 \rightarrow 17$
$l = -38 \rightarrow 41$

Refinement

Refinement on F
$R = 0.0364$
$\omega R = 0.0352$
$S = 1.1237$
4375 reflections
356 parameters
Only coordinates of H atoms refined
Method, part 1, Chebychev polynomial,
(Carruthers & Watkin, 1979, Prince, 1982)
[weight] = $1.0/[A_0*T_0(x) + A_1*T_1(x) \ldots + A_{n-1}]*T_{n-1}(x)]$
where A_i are the Chebychev coefficients
listed below and x = Fcalc/Fmax Method

$(\Delta/\sigma)_{max} = 0.015798$
$\Delta\rho_{max} = 2.04$ e Å^{-3}
$\Delta\rho_{min} = -0.75$ e Å^{-3}
Extinction correction: none
Scattering factors from International
Tables Vol C 4.2.6.8 and 6.1.1.4
Absolute structure: Flack (1983), 2818
Friedel-pairs
Flack parameter = 0.010 (8)

= Robust Weighting (Prince, 1982) W = [weight] * [1-(deltaF/6*sigmaF)^2]^2 A_i are: 1.25 -0.227 1.03

Table 1. Selected geometric parameters (Å)

Br18—C7	1.913 (4)	C3—O14—C15	115.1 (3)
Br118—C107	1.916 (4)	C102—O101—C110	112.8 (3)
O1—C2	1.441 (5)	C103—O104—C105	113.4 (3)
O1—C10	1.437 (5)	C102—O111—C112	114.4 (3)
O4—C3	1.423 (5)	C103—O114—C115	115.5 (3)
O4—C5	1.421 (5)	O1—C2—O11	109.9 (3)
O11—C2	1.408 (5)	O1—C2—C3	109.6 (3)
O11—C12	1.436 (5)	O11—C2—C3	104.8 (3)
O14—C3	1.408 (5)	O1—C2—C13	104.6 (3)
O14—C15	1.421 (5)	O11—C2—C13	114.8 (3)
O17—C6	1.426 (5)	C3—C2—C13	113.3 (4)
O19—C9	1.422 (5)	C2—C3—O4	110.4 (3)
O101—C102	1.402 (5)	C2—C3—O14	104.3 (3)
O101—C110	1.439 (4)	O4—C3—O14	110.4 (3)
O104—C103	1.433 (5)	C2—C3—C16	112.4 (3)
O104—C105	1.438 (4)	O4—C3—C16	106.0 (3)
O111—C102	1.423 (5)	O14—C3—C16	113.4 (3)
O111—C112	1.430 (6)	O4—C5—C6	107.6 (3)
O114—C103	1.404 (5)	O4—C5—C10	110.2 (3)
O114—C115	1.427 (5)	C6—C5—C10	111.9 (3)
O117—C106	1.411 (5)	C5—C6—O17	112.6 (3)
O119—C109	1.424 (4)	C5—C6—C7	107.9 (3)
C2—C3	1.565 (6)	O17—C6—C7	107.5 (3)
C2—C13	1.507 (6)	C6—C7—Br18	115.1 (3)
C3—C16	1.516 (6)	C6—C7—C8	126.4 (4)
C5—C6	1.526 (5)	Br18—C7—C8	118.4 (3)
C5—C10	1.511 (5)	C7—C8—C9	122.1 (4)
C6—C7	1.502 (6)	C8—C9—O19	108.2 (3)
C7—C8	1.322 (5)	C8—C9—C10	111.3 (3)
C8—C9	1.503 (6)	O19—C9—C10	111.4 (3)
C9—C10	1.499 (6)	C5—C10—C9	111.3 (3)
C102—C103	1.554 (5)	C5—C10—O1	109.5 (3)
C102—C113	1.529 (6)	C9—C10—O1	108.4 (3)
C103—C116	1.516 (6)	O111—C102—O101	110.7 (3)
C105—C106	1.516 (5)	O111—C102—C103	104.6 (3)
C105—C110	1.518 (5)	O101—C102—C103	111.4 (3)
C106—C107	1.506 (5)	O111—C102—C113	112.4 (3)
C107—C108	1.306 (5)	O101—C102—C113	105.7 (3)
C108—C109	1.528 (5)	C103—C102—C113	112.1 (3)
C109—C110	1.515 (5)	C102—C103—O104	109.5 (3)
		C102—C103—O114	104.2 (3)
C2—O1—C10	113.8 (3)	O104—C103—O114	110.5 (3)
C3—O4—C5	114.3 (3)	C102—C103—C116	112.6 (3)
C2—O11—C12	115.6 (3)	O104—C103—C116	105.8 (3)

O114—C103—C116	114.3 (3)	Br118—C107—C108	120.1 (3)
O104—C105—C106	108.1 (3)	C107—C108—C109	122.5 (3)
O104—C105—C110	108.9 (3)	C108—C109—O119	110.9 (3)
C106—C105—C110	112.9 (3)	C108—C109—C110	110.7 (3)
C105—C106—O117	113.8 (3)	O119—C109—C110	107.9 (3)
C105—C106—C107	107.7 (3)	C105—C110—C109	110.7 (3)
O117—C106—C107	111.7 (3)	C105—C110—O101	108.5 (3)
C106—C107—Br118	113.3 (3)	C109—C110—O101	107.0 (3)
C106—C107—C108	126.6 (3)		

Table 2. Hydrogen-bonding geometry (Å, °)

D—H···A	D—H	H···A	D···A	D—H···A
O17—H1···O1^{i}	0.84 (4)	2.26 (5)	2.900 (4)	133 (4)
O19—H2···O17^{ii}	0.98 (5)	1.96 (5)	2.848 (4)	150 (5)
O117—H3···O119^{iii}	0.85 (4)	1.87 (4)	2.714 (4)	173 (5)
O119—H4···O117^{ii}	0.79 (4)	2.17 (4)	2.815 (4)	139 (4)

Symmetry codes: (i) $1 + x, y, z$; (ii) $x - 1, y, z$; (iii) $1/2 + x, 3/2 - y, 1 - z$.

H atoms bonded to C were included at calculated positions and ride on their respective C atom.

Alcohol H atoms were refined positionally with restraints on O—H distances and C—O—H angles. Data collection: COLLECT (Nonius BV, 1997). Cell refinement: Denzo/Scalepack (Otwinowski & Minor, 1997). Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1997). Program(s) used to solve structure: SIR92 (Altomare *et al.* 1994). Program(s) used to refine structure: CRYSTALS (Watkin *et al.* 2003). Molecular graphics: ORTEP–II (Johnson 1976) in teXsan (MSC, 1992–1997). Software used to prepare material for publication: CRYSTALS (Watkin *et al.* 2003)